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## CANCER OF THE ESOPHAGUS

PORTER P. VINSON

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Cancer of the esophagus is the most common cause of dysphagia. Willy Meyer has stated that 90 per cent of the patients who come to him because of dysphagia have cancer. This percentage is considerably higher than what we observe at the Mayo Clinic, where only about 30 or 40 per cent of patients with dysphagia have cancer.

Women are much less often affected with cancer of the esophagus than men, the ratio of incidence being about 1 to 5. The location of the lesion also varies in the two sexes. In women, about 50 per cent of the lesions are at the introitus, in men, 50 per cent are 11 to 14 inches from the incisor teeth. Owing to the location of the lesion, metastatic nodules are more often demonstrable in women, because they appear in the cervical glands, whereas in men the first metastasis is to the mediastinum, and therefore nodules are not detectable.

An erroneous idea is prevalent regarding the degree of malignancy of cancer of the esophagus. It has been said that it is relatively benign. As a matter of fact it is very malignant, being of about the same degree as cancer of the cervix, which it resembles in behavior. In every case in which biopsy has been made, Broders has graded the cancer as 3 or 4. The reason the grade is considered low is because metastatic nodules are not demonstrated, but as has already been mentioned, the fact that they are not demonstrated does not mean that they

do not exist, they are simply at a point where they cannot be seen

The duration of life, with malignancy of the esophagus, is approximately fourteen months from onset to termination. Most patients have had symptoms for about seven months before coming to the Clinic, and they live another seven months.

It is interesting, also, that the patients fall into a rather definite economic group. Most of the men are farmers, truck drivers, or bar-tenders, that is, men who tend to be careless about their personal habits and who eat rapidly.

I have had two patients who have developed malignancy of the esophagus on preexisting benign strictures. Both strictures were caused in childhood by swallowing lye. One patient was burned at the age of eighteen months. When she was fifteen years old the stricture was dilated, following which she was quite ill for several months, then made a fair recovery. A diagnosis was made of lung abscess. As shown by the subsequent history, what really happened was a mechanical perforation into the bronchus. The patient came to the Clinic in January, 1923, at the age of thirty-eight. At that time she had an ordinary, apparently benign stricture of the esophagus (Fig. 162), which I dilated four or five times. Four weeks after the last dilation, when she swallowed fluid, it caused her to cough. She was running a fever, and returned to the Clinic. Not knowing the previous history of the probable perforation at the age of fifteen, I told her husband that we had seen one case in which cancer developed in the scar, and that his wife's stricture had behaved in a way that made me think it might be cancerous. He then told me about the trouble when she was fifteen years old, which seemed to explain the whole proposition. Fistula into the bronchus, with a tiny opening remaining, and thus stretching of the scar tissue had resulted in leakage. Gastrostomy was performed in this case. The stricture appeared to be benign with considerable granulation tissue. There was some bleeding. A piece of tissue was coughed up, and on examination proved to be inflammatory. Esophagoscopic examination was performed, a piano wire passed into the gastrostomy opening,

and the thread pulled up through the mouth. If the patient's condition improved, I planned to dilate the stricture further. After the gastrostomy she had a rather slow convalescence, but she gained weight from 64 to 100 pounds, and was getting on well, when she began to cough, and the cough increased until she developed bronchiectasis, and died eighteen months after the gastrostomy. This was thirty-six years after the lye burn had been received. At necropsy a very scirrhouss obstruc-

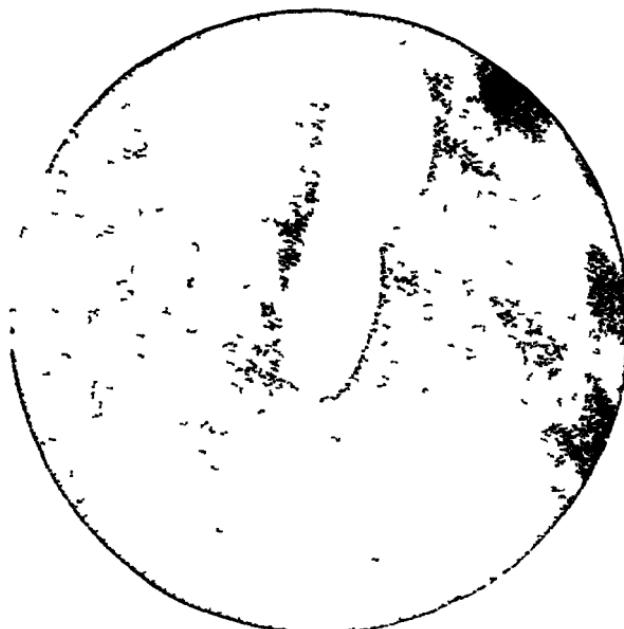


Fig. 162.—Carcinoma of the esophagus developing in the scar of a cicatricial stricture, which had resulted from the ingestion of lye

tion was found in the esophagus, extending into the hilum of the left lung. There was evidence of an old perforation into the left bronchus. This appeared to be fibrous inflammatory tissue, but a microscopic examination of a section proved it to be cancer.

The other case of malignancy of the esophagus originating in a previous burn was in a man who had received a burn in childhood. He had trouble in swallowing as he grew older.

When he came to the Clinic there were metastatic nodules all over his body skull, scalp, skin, muscle, and bone I have never seen more general metastasis, with such large nodules . He was sent home at once, and died soon after Tissue removed at necropsy proved to be malignant

#### TREATMENT

Many physicians advise early, routine gastrostomy in these cases of malignancy Others prefer radium and  $\tau$ -ray treatment, and certain enthusiastic thoracic surgeons advocate resection

It has been the policy in the Clinic, since we found that radium did not give relief, to dilate malignant strictures with ordinary sounds in the same way that we dilate benign strictures It is as easy to dilate a malignant as a benign stricture of the esophagus Only three splits of the esophagus have occurred in the last five years in about 500 cases of cancerous stricture treated in the Clinic During the same period, in a small group of cases in which dilation was not attempted, there have been three spontaneous perforations It is also remarkable that there has not been a single fatal hemorrhage following dilation, although hemorrhage is often the terminal event in cases of carcinoma of the esophagus

I dilate the strictures up to 45 F at the first treatment, then let the patients go home, instructing them to return for further dilations to keep the lumen patent and to maintain comfort. The treatment cannot cure, it does palliate, and the patients live in comparative comfort for as long as three years

Gastrostomy, on the other hand, is a nuisance to everybody Nearly all the patients we have seen on whom gastrostomy has been performed were sorry it had been done They can ill afford a long stay in the hospital and, as a rule, have nobody at home to take care of them The mortality following gastrostomy is ten times as great as that following dilation, and the patient does not obtain the same degree of relief, since he cannot swallow

However, there are certain types of malignant strictures that cannot be dilated, or in which dilation fails to afford relief

1 In cases of cancer of the introitus, with either unilateral or bilateral cord paralysis, metastasis to the cervical glands, and cough, no relief can be obtained by passing sounds. Neither is relief afforded by gastrostomy. The only thing to do in such cases is to make the patient comfortable by the liberal use of morphin

2 If the lesion is essentially gastric, and obstruction is produced by shelving of the malignant growth at the cardia, sounds pass over this mass, and no real stretching is accomplished, so that this method of treatment is of little value. Gastrostomy in such cases may result in metastasis to the abdominal wall at the site of the old incision, and add permanently to the patient's discomfort

3 Spontaneous perforation into the bronchus or into the trachea makes dilation inadvisable. In such cases the thread will wrap around the esophagotracheal septum, and the sound cannot be guided. Gastrostomy is then possibly indicated, but should not be urged

Results with radium have been absolutely disappointing. A few men have reported good results following  $x$ -ray treatment. There are two outstanding dangers with  $x$ -ray: the patient is incapacitated after treatment by nausea and vomiting, and there is a chance of producing pulmonary fibrosis with respiratory symptoms. I do not advise  $x$ -ray treatment unless the patient is in very good condition. Surgery is purely experimental and should not be advised.

I have recently observed one case of malignancy developing in the sac of a pharyngo-esophageal diverticulum. An attempt was made to remove the sac, but the lesion extended too far.

Ninety per cent of the cases of cancer of the esophagus can be diagnosed on the history alone. If the patient is a man more than forty years of age, and has had progressive and constant dysphagia for a year or less, beginning with solid food, later with semi-solids, and finally with liquids, with or without pain, and without a history of swallowing a caustic, the diagnosis

is cancer. Symptoms of cancer are simply mechanical, the condition is advanced before dysphagia begins. Early recognition is impossible, unless a routine esophagoscopy is made in all cases, which, of course, would not be practicable. The lumen of the esophagus must be narrowed sufficiently to obstruct a bolus of solid food before cancer of the esophagus can possibly be recognized.

Patients with cancer have pain, but not the colicky pain characteristic of cardiospasm. Pain is very rare in early cases of cancer, and when it develops, late in the disease, it is a misery, whereas the pain of cardiospasm is sharp, resembling that due to gall-stones, and appears early. Sometimes cardiospasm is diagnosed as gall-stones for this reason.

The  $\tau$ -ray is of value in diagnosis, in that, when positive, it shows a very typical picture: a moth-eaten, irregular appearing lesion. On the other hand, there may be malignancy with a perfectly smooth obstruction. The  $\tau$ -ray is also of value in determining perforation into the bronchus. If there is a history of cough after swallowing liquids, a preliminary  $\tau$ -ray examination should be made. Most patients should have an x-ray examination unless they are having difficulty in swallowing liquids, in which instance it is inadvisable to give them barium if dysphagia is pronounced, because it may complete the obstruction. Then gastrostomy must be considered, or the patient sent home without treatment. The thread should be swallowed before the  $\tau$ -ray examination is made, because the barium may make it impossible to pass the thread.

The passage of sounds is also helpful in diagnosis. The sound is passed on the thread down to the obstruction, which can be felt with the sound as well as if a finger were on it. The obstruction due to cancer is firm and inelastic, a type which is not characteristic of benign stricture. On passage of the first sound a pink-tinged mucus is obtained. This mucus is intimately mixed with blood, not blood-streaked. Cancerous strictures can be dilated up to 45 F without difficulty. This is not true of benign strictures.

It is not difficult to remove a specimen through the esophago-

scope for biopsy, but it delays the patient for another day. Most patients are referred for dilation the morning after they register, and are dismissed that afternoon, so that they have to remain only thirty-six to forty-eight hours. We advise them to return if they need any further dilation.

#### EXAMINATION OF CASES

**Case 1**—This patient is fifty-eight years old. She has had practically constant, severe pain in the midsternum which radiates through to the back, since March, 1923. The pain is not related to the ingestion of food. She has pain when food passes a certain place in the esophagus, but never has had regurgitation or vomiting. She is afraid to eat anything, has been living on liquids for the last two months, and is losing strength and weight. During the last two months, the pain has settled in the left lower chest, but it is present over the entire chest.

The x-ray revealed malignancy of the stomach, which is encroaching on the lower esophagus. I don't know how much we can expect to accomplish in such a case. The patient started this thread day before yesterday, before the x-ray was taken, because of the fact that she was swallowing liquid only. The thread did not prove to be necessary in this case, but the precaution is worth while whenever there is the possibility of complete closure following the taking of barium. In dilating, first I use a blunt olive on a whale bone staff, which is passed over the thread, to the obstruction, but without pressure. The obstruction is right at the cardia, but unfortunately I shall not be able to proceed with the dilation, because the thread has snarled and broken. This illustrates the difficulty we often have with older patients: they do not follow directions. We told her to swallow only five yards, and she has swallowed ten. The result is a snarl, and a day's delay.

**Case 2**—This patient is fifty-nine years old. He has had dysphagia for six months. Before that, he was healthy. Difficulty began with swallowing solid food, and there has been constant progressive dysphagia ever since. The onset was rather sudden. The patient's diet is now restricted to a very small amount of fluid. For that reason a sound is passed on a thread before he is referred for an x-ray. He started taking the thread yesterday afternoon, and has swallowed it exactly as he was instructed. The obstruction is in the middle third, 11 5 inches from the esophagus. The lesion is very solid, almost like bone, and is evidently very scirrhouous. The thread is pulling up through the stricture because the patient did not have twenty-four hours in which to swallow it. Therefore the dilation will not be done until tomorrow, as it should not be attempted with a loose thread.

This is the first case I have ever seen of a probable malignancy of the esophagus in which the wire spiral could not be passed with ease. I have seen a number of benign strictures in which this was not possible.

*Next day*—I am afraid this patient has an esophagobronchial fistula with his thread through it. I mention this because it illustrates that, no matter how careful one is, unexpected difficulties may arise. In every case

of cancer of the esophagus I ask the patient, before I give him the thread, whether he coughs after swallowing liquids. If the reply is affirmative, an x-ray is taken to detect a possible fistula before the thread is swallowed. This man, however, replied in the negative. Yesterday I met obstruction at the lesion, so dense that I couldn't get the wire spiral through. This morning when the patient came in he said that he had coughed considerably last night. On further questioning he said that for several weeks he had had considerable cough after swallowing liquids, although he answered in the nega-



Fig. 163.—Carcinoma of the esophagus with perforation into left main bronchus. Note barium in descending bronchi.

tive yesterday. This shows the unreliability of the first history. It is, therefore, likely that he has an esophagobronchial fistula and that the thread has passed through the opening into the bronchus, has been coughed up and reswallowed. This would explain the obstruction to the wire spiral at the level of the lesion.

I have never seen a case in which the thread went through the perforation that could not be diagnosed immediately on pulling up the thread. In such a case not more than 6 to 8 inches of the thread can be pulled up before it becomes perfectly tight and at the same time produces paroxysms

of cough I can pull this patient's thread up 3 or 4 feet, and he does not cough Therefore, I may be mistaken in thinking there is a fistula On passing sounds, there is some snubbing of the wire spiral at the point of obstruction, but no difficulty in stretching the rather long malignant stricture to 45 F The patient is coughing up considerable blood If he has a fistula into the bronchus, the thread fortunately did not pass into the perforation \* I shall refer him for x-ray examination this afternoon, to determine the question of perforation (Fig 163)

**Case 3**—This patient is just the type for whom dilation offers most He has no relatives, no place to go, no money If I referred him for a routine gastrostomy, there would be nobody to take care of the tube As a result of dilation, he will enjoy several months of relief He is fifty-two years of age Five years ago, his esophagus felt raw, and he had trouble for a few months, then got better Last fall the same trouble recurred, and for the last two months his food has stuck in the lower third of the esophagus He has been able to work only part time He can take warm water slowly, and a little bread, but not much solid food He has lost 23 pounds in weight, and appears cachectic X-ray examination has not been made I examined him yesterday afternoon, and started a thread at once He did not follow my instructions, and has swallowed too much of it A snarl has resulted, and the thread is not taut An unguided sound snubs at the upper edge of the obstruction, and if an attempt were made to pass the sound with pressure, a hole might be punched in the wall of the esophagus Therefore, I will tie a fresh thread to the one that he has partially swallowed, and have him take it more slowly until three or four yards have been ingested

Patients if given plenty of time, and if they follow directions, will rarely have difficulty in getting the thread down satisfactorily It should not be taken faster than about a foot an hour, or it will snarl Twenty-four hours is allowed to swallow five yards Button-hole twist, size D, is used

**Next day**—The thread is now taut Before dilating, I measure off the distance of the obstruction from the incisor teeth, on the whale-bone staff In this case it is 14 inches I mark that distance on the staff with a small strip of adhesive tape, and in passing the sound exert no pressure until the spiral has passed that point A small piece of tissue was caught in the spiral during dilation, and on microscopic examination proved to be Grade 3 squamous-cell epithelioma The patient returned home the day following dilation, in relative comfort

**Case 4**—This patient has had dysphagia for six months, and prior to that he had had indigestion of an indefinite type He has had gas on the stomach for the last four years Dysphagia began with the ingestion of solid foods, and has been constant and progressive The patient can still swallow soft foods, but has to take them very slowly He has no pain, but has lost 30 pounds in weight in six months There is a small amount of mucus in the throat

A typical malignant lesion of the esophagus was revealed fluoroscopically

\* The x-ray examination revealed a fistula from the malignant esophageal stricture into the left bronchus

ally, but there was not enough obstruction to make satisfactory plates. This is one reason for errors in diagnosis from x-ray examination alone. Unless the lumen is so constricted as to cause almost complete obstruction, cancerous lesions are likely not to be detected in the plates, because the barium will not be retained sufficiently to demonstrate them. The plates may even be negative, but fluoroscopically the lesions can usually be detected.

This obstruction is high in the esophagus, 9.5 inches from the incisors. The patient could feel his food sticking high. In fact, patients can very often locate the stricture accurately. Following the passage of the first sound, there is usually considerable bleeding. A piece of tissue picked up in the end of the spiral proved on microscopic examination to be Grade 3 squamous-cell epithelioma. The stricture was easily dilated to 45 F.

## PYLORIC OBSTRUCTION DUE TO SWALLOWING A SOLUTION OF CONCENTRATED LYE

PORTER P VINSON AND HOWARD R HARTMAN

The swallowing of a solution of lye almost always results in a burn of the esophagus severe enough to produce a cicatricial stricture. In fatal cases, a scarring of the mucous membrane of the stomach is sometimes noted, but a stricture the result of a burn at the pylorus is exceedingly rare. Such a burn usually follows the ingestion of a large quantity of the solution in attempting suicide. The following is an illustrative case.

A woman, aged fifty-one years, was admitted to the Mayo Clinic September 30, 1923, with a history of having vomited at irregular intervals for three years. On September 4 she had swallowed a solution of lye, probably with suicidal intent. For ten days there was moderate dysphagia followed by one week of normal deglutition, when continuous vomiting and inconstant abdominal pains ensued.

At the time of examination the patient was greatly emaciated, and marked peristalsis was visible. The temperature was 100.5°. An attempt was made to pass a stomach tube because the patient said that she could swallow without difficulty, but the tube met with an obstruction in the upper esophagus. The x-ray examination revealed an obstruction in the upper third of the esophagus (Fig. 164). The patient then swallowed a twisted silk thread, and by the use of this as a guide for an esophageal sound, a stricture was located 8 75 inches from the incisor teeth, the esophagus was involved from this point through the cardia. After the passage of sounds, the patient expectorated a considerable amount of foul purulent material, and it was assumed that the temperature was caused by esophagitis and peri-esophagitis, possibly associated with a mediast-

tinal abscess. The fever continued for three months, rising as high as 102°. The stricture was gradually dilated to 32 French, resulting in marked improvement in the patient's general condition and complete relief from vomiting. It was always difficult for the patient to swallow the thread, and usually required three or four days for the thread to become anchored sufficiently taut in the intestine to permit the passage of sounds.



Fig. 164.—Partial esophageal obstruction in the upper third.

March 21, 1924, the stricture was dilated without difficulty, but four days later vomiting again ensued. The patient returned to the Clinic April 14 in a semi-comatose condition. She had lost much weight, and her abdomen was distended. She was in pain, vomiting, and dehydrated. The vomitus was foul and bile-stained. A stomach tube could be freely passed. The presenting condition was obstruction in the gastro-intestinal tract, but because of the patient's very poor condition, examinations were limited. Roentgenograms were not made. Supporting measures of proctoclisis of 5 per cent glucose subcutaneous

and intravenous saline, intravenous glucose, and blood transfusions, were carried out, but the patient died April 26



Fig 165—Extensive scarring of the esophagus from caustic

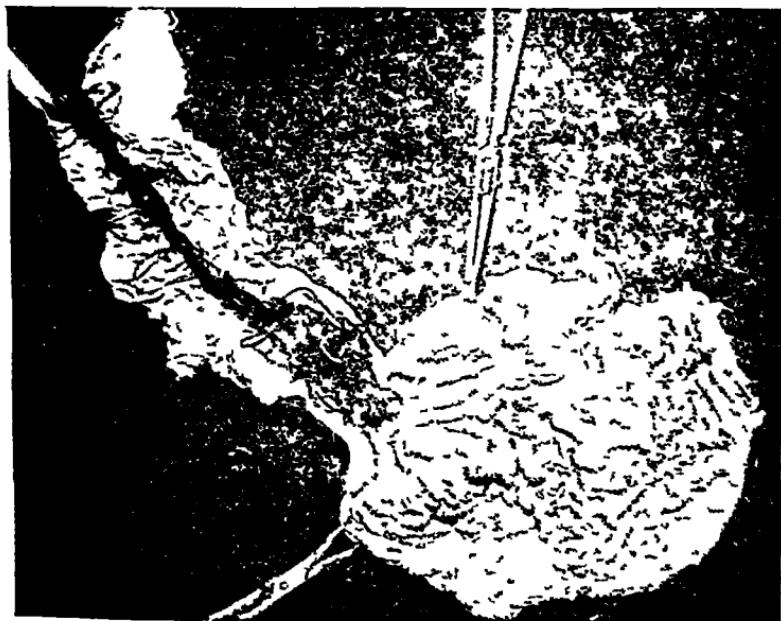


Fig 166—Stricture of the pylorus with impaction of silk thread producing complete obstruction

Postmortem examination revealed a scarring of the lower two-thirds of the esophagus, with considerable peri-esophageal

fibrosis (Fig. 165) The lumen of the esophagus was sufficiently large to have permitted the free passage of food The external appearance of the stomach was normal, but on opening the organ, there was found to be considerable scarring of the mucous membrane of the lesser curvature, and an annular stricture of tense fibrous tissue greatly narrowing the lumen at the pylorus (Fig. 166), this was occluded by the previously swallowed thread which had snarled in the stomach The free end of the thread projected into the intestine, so that there was complete obstruction to normal peristalsis, but not to reverse peristalsis

## PEPTIC ULCER AND PALPABLE MASSES

HOWARD R. HARTMAN

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A history of a gastric complaint and a palpable mass in the upper abdomen is almost diagnostic of gastric cancer, as 95 per cent of such masses prove to be malignant. Occasionally, however, an accurate x-ray examination which reveals a benign lesion, may substantiate the clinical history so that a diagnosis of peptic ulcer, with an inflammatory mass, can be made. This differential diagnosis is of great importance to the patient because operative interference, if undertaken too soon and without the proper preparation of the patient, is likely to prove fatal. If the patient receives proper and ample preoperative preparation, the inflammatory masses subside and operation is then conducted without the danger of infection and the too frequent sequelae. To arrive at the correct diagnosis in such cases, one must weigh all the clinical evidence and not forget the high incidence of malignancy, but if the patient's general condition is good, the classical indications of carcinoma are lacking and there is clinical evidence to support the diagnosis of ulcer, one is justified in the diagnosis of an inflammatory condition subsequent to ulcer, particularly if confidence can be placed in the x-ray diagnosis. As illustrative of this type of case, and to compare the effect of hasty operation with the results of proper preoperative care, two case reports are presented.

Case 1.—A man, aged sixty years, had had various gastric complaints since he was sixteen, but without characteristic diagnostic importance until fourteen years before coming to the Clinic, when he began to have periods of dull pain around the umbilicus, one-half to one hour after meals. This was relieved at times by food and soda. It lasted from a month to six weeks, and then would subside for from one to twelve months. Some periods were not so sharply defined. Six months before the patient came to the Clinic, the gastric symptoms gradually increased. The pain was related to meals as before, but became dull and gnawing and was distributed throughout

the abdomen. It was relieved by food and soda. There was no spontaneous vomiting, but if induced, it gave relief from the pain.

On physical examination the patient showed slight general weakness. He had lost 6 pounds in six months. Just to the left of the umbilicus, there was a mass 4 by 6 cm, which was tender. The leukocyte count decreased under treatment from 18,500 to 11,200. Gastric analysis revealed a total acidity of 60, free hydrochloric acid 40, and total content of 450 c.c. The x-ray report was perforated gastric ulcer on the body of the stomach, and apparently healed tuberculosis in both lungs.

The patient was treated preoperatively, in a hospital, first for pyloric obstruction, consisting of rest in bed, a liquid noncoagulable diet, gastric lavage twice a day, and proctoclysis of 1000 c.c. of 5 per cent glucose. Normal saline did not seem to be indicated. The proctoclysis was well absorbed. The pylorus was partially patent. The 450 c.c. of gastric content being due to retention and hypersecretion. In three days the mass was reduced one-half. The patient was then placed on an alkalinization form of treatment with milk and alkalis. Seven days later the mass was barely palpable. Gastric lavage was no longer indicated. One-third of the stomach was resected, including the ulcer which was surrounded by much inflammatory exudate. The size of the ulcer made resection advisable. The pathologic report on the tissue removed was simple perforating type of ulcer associated with marked subacute inflammation and edema. The patient died four days later. Necropsy disclosed the principal cause of death to be peritonitis and renal insufficiency. There was no preoperative clinical evidence of defective renal tissue.

Case 2.—A man, aged thirty years, had gastric trouble for about four years. It was of an indefinite nature for two years. At the end of another year, he went to a hospital because of vomiting. At this time he had colicky pain in the epigastrum after meals, it was relieved by vomiting. Food or alkalis had never been tried for relief. The patient was also subject to burning in the stomach, associated with a regurgitation of sour material. He improved, but had to re-enter the hospital in a month, where alkalinization treatment, consisting of milk and powders, with gastric lavage, was carried out. Six months of careful dieting after leaving the hospital, relieved all symptoms, but six months later and ten days prior to his registration at the Mayo Clinic the pain and vomiting returned. Everything was vomited, including water.

On physical examination, appreciable loss of strength was evident. The patient had lost 26 pounds in two years. The systolic blood pressure was 120, and the diastolic, 60. To the right of the umbilicus was an easily palpated movable mass about 7 cm in diameter, and very tender. The gastric content was 1500 c.c., with a total acidity of 70, and free hydrochloric acid, 50. No leukocytosis was found. The treatment employed in the previous case was carried out. After three days it was not possible to palpate the mass, and gastric lavage was no longer indicated. Alkalization of the previous content with milk and powders was continued for two weeks, but even on markedly increasing the alkalis the content was still highly acid. At opera-

tion a subacute perforating ulcer was found immediately above the pylorus, with considerable evidence of subacute inflammation around the pylorus. Because of the possibility of malignancy, a partial gastrectomy was performed. The immediate and final pathologic reports on the tissue removed read "chronic gastric ulcer."

There was in this case still "considerable" evidence of subacute inflammation, which no doubt a few days earlier would have been much more in evidence. These inflammatory masses subside, as a rule, very rapidly on the treatment outlined, and, if it is continued long enough, not only does the mass disappear, but the inflammatory reaction itself is reduced to a point where surgical intervention can be carried out, so that the mortality will be no greater than is to be expected for the particular kind of operation that is ultimately indicated. Great care must be used in selecting the proper cases. If there is gastric obstruction, the preparation indicated is a liquid, noncoaguable diet (unless the obstruction is complete), lavage twice daily, proctoclysis of glucose, and perhaps saline hypodermoclysis, even if the obstruction is due to malignancy.

From forty-eight to seventy-two hours usually suffices to get the stomach clean, increase the tonicity of a dilated organ, and sometimes to relieve at least that part of a pyloric stenosis due to inflammatory swelling. Also during this time the usual dehydration that accompanies pyloric obstruction is overcome by the liquid diet and the injection of fluids. The kidney output is improved and many toxic elements are eliminated from the blood. When the stomach is clean and the dehydration is corrected it removes the added danger of operating in the face of pyloric obstruction. One must be very certain of his ground to continue the preoperative treatment much longer because of the high incidence of carcinoma when there is a history of gastric trouble and a palpable mass. Yet with proper care to the right patient the treatment of a peptic ulcer with a palpable mass should continue, as the mass is easily reducible and even the infection causing the mass is reduced so that the danger of postoperative peritonitis is eliminated and operative mortality is reduced to normal for the particular surgery ultimately indicated.



## SPONTANEOUS HEALING OF CHRONIC DUODENAL AND GASTROJEJUNAL ULCER

GEORGE B. EUSTERMAN

Two cases are presented with laboratory data, illustrative of spontaneous healing of a duodenal and a gastrojejunal ulcer, respectively. Clinical and pathologic observations on the capacity of chronic peptic ulcers for healing are based on accumulated evidence in untreated, medically treated, surgical, and post-mortem cases. Factors which retard or prevent healing are discussed.

Case 1.—A man, aged sixty-one years, was examined in the Clinic August 4, 1924, with a presenting complaint of "nervousness." He had been married in 1889, and his wife had died, presumably of tuberculous peritonitis, in 1918. About one year after her death he had a "nervous breakdown." This had its inception as a sinking feeling when he retired, and on account of this he would often get up for a variable period shortly after retiring. Soon he developed a fear of going to places or meeting people, and had a strong aversion to accepting any form of responsibility. This psychasthenia still persisted at the time of examination. He had never been robust or a sound sleeper, but grew stronger *pari passu* with age. Malaria in childhood and an uncomplicated gonorrhea at twenty-five, were his only previous illnesses. His father died of pulmonary tuberculosis at the age of forty-four, and his mother lived to the age of eighty-three. He had been in many occupations and trades until three years before. Since then he had done nothing, had no desire to do anything, and time consequently hung heavily on his hands. He had an income sufficient to live on comfortably. Barring an occasional headache, he had no complaints. On further questioning he recalled that thirty years before, for a period of two or three years, he had "stomach trouble," for which he was treated by various physicians, each treating and diagnosing his ailment differently. However, these gastric disturbances were intermittent, periods of distress alternating with periods of complete relief. During an exacerbation a gnawing, burning mid-epigastric pain would appear three or four hours after meals, invariably at 10 a.m. and 4 p.m., and would be relieved by alkalies, alimentation, or by lying down. This pain was most marked in the afternoon, and usually 0.5 dram of soda would give relief. There was no history of acute colicky pain or of gross

hemorrhage from the stomach or bowel. Nervous or emotional strain, or dietary indiscretions would aggravate his symptoms or bring about an "attack." By eating carefully of bland foods for several years, beginning soon after the onset of his trouble, he had improved gradually until recovery was complete. He had had no disturbing gastric symptoms in the last twenty-seven or twenty-eight years, and had eaten the same food as the average healthy person. When quite nervous he would belch occasionally soon after a meal.

As the patient's chief concern was his nervous condition, it was difficult at first to induce him to submit to laboratory investigation of his upper diges-

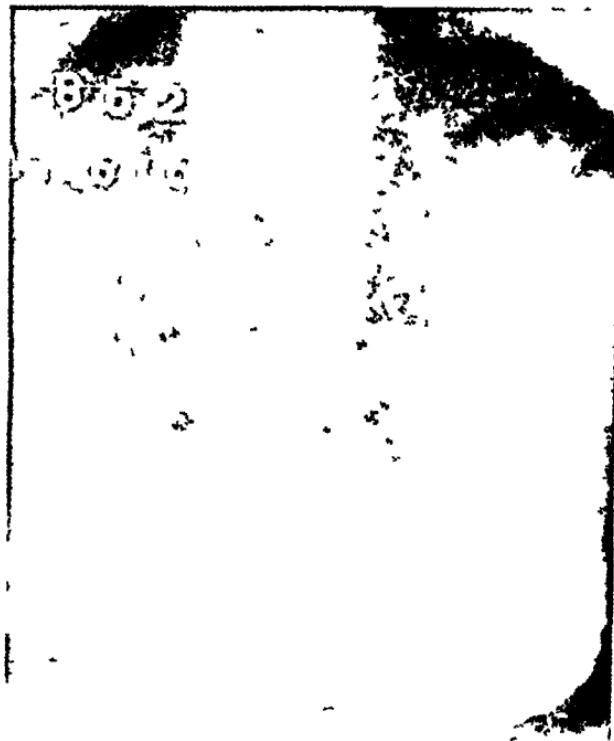


Fig. 167.—Roentgenogram of stomach, showing characteristic deformity of the duodenal cap.

tive tract. Gastric analysis revealed a total acidity of 60, and a free hydrochloric acid of 18. The quantity expressed was 60 c.c., the chemical reaction for blood was negative. Fluoroscopic screen examination, and roentgenograms revealed a persistent deformity of the duodenal bulb, characteristic of duodenal ulcer (Fig. 167). The general physical examination was satisfactory, barring exaggerated reflexes, moderate arteriosclerosis, malnutrition, and moderate prostatic hypertrophy. The hemoglobin per cent was 79, and the

leukocytes numbered 6,900. The Wassermann reaction on the blood was negative. The dental films showed definite periapical infection in three devitalized teeth.

It was only by the routine inquiry into past illnesses, injuries, habits, and so forth that the history of intermittent gastric disturbances occurring thirty years ago, over a period of two or three years, was elicited in this case. I think you will agree that the patient's trouble had all the ear-marks of the accepted syndrome of ulcer. This, with the fact that a characteristic deformity of his duodenal cap was revealed on fluoroscopic examination, and in all the roentgenograms should justify the diagnosis of a chronic healed duodenal ulcer. The question might be raised: Why does the cap deformity still persist if the ulcer has been quiescent and healed for twenty-seven or twenty-eight years? In my experience this is the rule in cases of duodenal ulcer, after successful medical or surgical treatment. It is exceptional for such ulcers to heal without some constriction or deformity of the lumen. Fluoroscopic examinations of clinically well patients, who years ago have undergone gastro-enterostomy for such a lesion invariably reveal a persistence of the original cap deformity. In the majority of cases, in fact, the absence of such a deformity in the cap or for that matter in the stomach, in patients who continue to complain after a gastro-enterostomy is reliable evidence that an ulcer never was present. I believe that many other instances of this kind can be found if patients who in the past have had a dyspepsia characteristic or suggestive of ulcer undergo a routine laboratory examination. There is no question but that in the majority of cases reliable clinical evidence, with positive roentgen findings by an experienced and expert fluoroscopist, "constitutes a veritable necropsy *in vivo*." Then we will not have to wait until necropsy reveals healed lesions and their sequelæ, which are erroneously regarded as having given rise to no symptoms during life.

Case 2 illustrates another type of lesion, far less common and more difficult of spontaneous resolution than the preceding one.

Case 2.—A man, aged fifty-eight years, presented himself at the Clinic a fourth time for examination, September 21, 1923, because of disability resulting from a fracture of his left hip in August, 1922. On May 4, 1904, a posterior gastro-enterostomy for a large chronic duodenal ulcer, was performed in the Clinic. The ulcer was 2.5 cm. in diameter, and situated 1.9 cm. below the pylorus on the anterior surface of the duodenum. A chronically inflamed appendix was also removed. The patient recovered uneventfully. In November, 1913, he returned for a second examination because of a right inguinal hernia. He made no complaints with regard to his stomach. Fluoroscopic examination at that time showed the gastro-enterostomy to be functioning normally, and nothing was seen passing the pylorus. A hernotomy was performed. In November, 1921, the patient returned on account of backache and "stomach trouble." The former was found to be due to a tuberculous arthritis and tilting of the fourth and fifth lumbar vertebrae. For about nine years he had had "spells of indigestion", characterized by aching, burning pain in the lower epigastrum, appearing from two to three hours after meals, associated with some belching and bloating. There had been no nausea, vomiting, bleeding, jaundice, fever, or paroxysmal pains. Soda, and a bland light meal relieved him. The pain also occasionally awakened him at night. Hot bread, doughnuts, heavy or fat food aggravated his distress. He was constipated.

Gastric analysis revealed a total acidity of 50, free hydrochloric acid 38, a trace of bile and a filtrate measuring 230 c.c. Roentgenograms of the stomach showed the anastomotic opening to be completely obstructed, and the pylorus open. There was moderate dental sepsis and the tonsils had been removed previously.

From these findings, and the nature of the complaint, a diagnosis of gastrojejunal ulcer was made. The patient was placed on an ambulant regimen for ulcer, which he followed for only a brief period as he was feeling fairly comfortable.

On the patient's final visit, in September, 1923, he did not complain of his stomach except that after an unusually hearty meal he was slightly distressed. Re-examination at this time did not reveal unusual findings. Gastric analysis by the fractional method showed a low hydrochloric acid titer, ranging from 0 to 14, and a maximal total acidity of 26, the filtrate measured 170 c.c. and was negative to Congo. Fluoroscopic examination at this time showed the gastro-enterostomy to be quite patent, the pylorus open, and deformity of the duodenal cap, the site of the original ulcer. The patient returned home on an ulcer regimen, including alkalis, which he persisted in for only two months. A letter received from him November 7, 1924, stated that he was free from gastric symptoms.

Those familiar with the late results of gastric surgery realize that anastomotic or jejunal ulcers are among the most formidable of complications. They tend to progress in extent, and often to perforate. On that account the majority are more resistant

to treatment than the primary lesion, or after a variable period of improvement and apparent cure, break down again with a recurrence of the usual symptoms. However, surgeons and internists with a large experience in this field are aware of the fact that the many early or late temporarily painful recurrences after gastrojejunostomy are really due to anastomotic ulcers which, for a variable period, are active and then heal. Surgeons, in the last two decades, have from time to time called attention to this fact, often attributing resolutions to the extrusion of mechanical devices or unabsorbable suture material from the anastomotic area. Approximately 5 per cent of our gastro-enterostomized patients give clinical evidence of such a complication arising, in about 2 per cent of whom a secondary operation or intensive treatment is instituted. Gastrojejunal ulcers may also cause a reactivation of healed, or partially healed, primary duodenal ulcers, which as a rule are not excised at the original operation. In Case 2 it is interesting to note that the patient was practically free from symptoms for a year prior to his third examination, and yet it was at this time that roentgen examination showed the stoma to be completely obstructed. While probably not true in this instance, such closures are often of a temporary nature, the result of spasm or edema provoked by the ulceration. The subsequent course of the condition, with virtually no treatment, was gratifying, and in my experience is unusual under the circumstances, especially when symptoms have been present over such a long period.

There is as yet no unanimity of opinion as to the permanence of healing of chronic gastric ulcer following medical management. The criterion of healing with most writers is the absence of symptoms and the disappearance or diminution of the niche. An increasing number of cases reported in contemporary literature by competent observers will enable us, in the near future, to determine the efficacy of medical treatment. The duration, type and extent of the lesion, and in lesser degree, the age and sex of the patient, must be taken into account. As seen at operation, four types of gastric ulcer may be distinguished: (1) small shallow, mucous erosions and minute slit-like ulcers,

(2) penetrating or perforating ulcers with very deep craters, (3) perforated ulcers, with or without an accessory cavity, and (4) carcinomatous ulcers. In my judgment, mucosal and the small penetrating ulcers of not more than two or three years' duration clinically, respond promptly and favorably to an intensive and thorough regimen. The older, more calloused penetrating or perforating type of lesion can only heal with the greatest difficulty, if at all. Such extensive perforated, calloused lesions, in which the base is formed by the interposition of a viscous such as the pancreas or liver, or with an accessory pocket, respond unfavorably to nonsurgical methods of treatment. Early small gastric lesions respond more completely and promptly to treatment than do those in the duodenum, as a rule. The early disappearance of the niche in the first few weeks of treatment is no criterion of healing, as it is invariably due to a plug of mucus in the crater, or in whole or in part to a diminution or disappearance of regional spasm. In the light of our present knowledge no gastric ulcers should be regarded as medically cured until symptoms and filling defect have been consistently absent for at least three years. In view of the persistence of the cap deformity in most cases of healed duodenal ulcer, it will be interesting to determine how frequently and to what extent the filling defect or niche persists after complete healing of a gastric ulcer.

Our knowledge concerning the capacity of an ulcer to heal after an operation by a skilful and experienced surgeon is quite complete. It must always be remembered that approximately 70 per cent of all ulcers are duodenal, and that gastro-enterostomy will be the *operation of choice* in the majority of cases by most of our representative surgeons, the present tendency toward excision and some form of plastic operation or resection notwithstanding. Following such operation the ulcer, whether single or multiple, invariably heals promptly. Reactivation may occasionally be encountered in the young adult, the highly nervous person, or anyone who is indiscreet in eating, drinking, or smoking. Extensive focal infection is undoubtedly a cause for reactivation of the original ulcer, or the formation of new

ulcers, but it is surprising how many persons who do not coöperate remain well after operation, especially elderly persons, with long-standing indurated or stenosing lesions. Until a decade ago, excision of gastric ulcers by knife or cautery was not so commonly practiced as now. Gastro-enterostomy alone for gastric lesions remote to the pylorus was followed by cure or improvement in only about 65 per cent of cases. The remainder had evidence of recurrent activity, and a few even progressed to hour-glass deformity, hemorrhage or malignant degeneration, but rarely to perforation. In recent years we have even found it necessary to perform a wide resection for large, chronic, perforated ulcers of the posterior wall and for most gastrojejunul ulcers, in order to conserve the ultimate health of the patient. These facts show how formidable and persistent certain types of gastric lesions may be. Repeated observation has convinced me also that in the bleeding type of ulcer healing does not necessarily insure against further hemorrhage, and that under certain circumstances or even without adequate cause hemorrhage may recur.

That chronic gastric and duodenal lesions have the capacity for spontaneous healing has been confirmed by the revelations at necropsy. In the past, many of the medical profession, the surgeon particularly, firmly believed that such ulcers would not heal unless dealt with surgically. The lessons gleaned from a review of our own postmortem material have been very instructive. Two thousand unselected necropsies between 1921 and 1924 revealed the presence of 378 ulcers, acute and chronic, some of which were healed. In 7 per cent there was concurrent ulcer of the stomach and duodenum, a percentage which closely approaches our surgical record of 6 per cent, that is to say, of every 100 patients having a calloused duodenal ulcer, six will have an associated gastric ulcer. There were 141 gastric and 244 duodenal ulcers, including twenty-nine healed gastric and ninety-four healed duodenal ulcers. Such ulcers involved several or all the walls of the viscus, mucosa, muscularis and serosa. In the group with healed ulcer, death had usually been due to other causes, in several, death followed surgical

interference on the stomach for marked motor impairment or actual stenosis. A history of gastric disturbances in the remainder had been the exception rather than the rule. However, this is not proof that these patients had not had a remote indigestion. Two other features of clinical interest should be mentioned: (1) out of the total of 378 postmortem cases with ulcer, the nature of the associated disease in order of frequency, and the main cause of death per se, or as a result of complications were as follows: diseases of the thyroid, chronic nephritis, prostatic hypertrophy, chronic cholecystitis, tumors of the brain and spinal cord, appendicitis, and gastro-enteritis of infants; (2) the average normal distance from pylorus to papilla of Vater is 7.9 cm., whereas in certain cases in which there were healed duodenal ulcers the distance had contracted to 6 cm. and less. This contraction causes a pouching of the first portion of the duodenum, as a rule unilateral. Such a pouching is often erroneously called a diverticulum.

That ulcers in various stages of development may heal spontaneously has been proved in various ways. In view of the information gleaned from Case 1, it is not unreasonable to assume that many persons, in whom definite scars were revealed in the stomach or duodenum at necropsy had a period of characteristic gastric disturbances during life. In connection with healed lesions seen at postmortem, Kantor has called attention to recent pathologic studies of Holzweissig, which tend to emphasize the tendency of peptic ulcer to heal spontaneously, and to explain the apparent infrequency of healed lesions at necropsy. This investigation, in a series of 1,759 routine necropsies, disclosed gastric or duodenal ulcer or scars in 6 per cent. The characteristic finding after a peptic ulcer has healed is a defect in the continuity of the muscularis mucosae. All other coats, including the epithelium, may be so completely restored as to give a superficially normal appearance to the former ulcer-bearing area, from which it may be inferred that pathologists did not find more healed ulcers in the past, not because the ulcers did not heal, but because they often healed so well that more than superficial inspection was necessary to reveal evidence of them.

## SUMMARY

The histories and subsequent clinical course of two patients with a chronic duodenal and a gastrojejunal ulcer, respectively, which healed spontaneously are reported. Other similar cases are observed from time to time.

It is predicted that routine clinical and laboratory investigation of persons who in the past have had painful gastric disturbances will often reveal positive evidence of quiescent or healed ulcers in the stomach or duodenum. It is very probable that many such healed ulcers found at necropsy are regarded as having given rise to no symptoms during life.

The incidence of spontaneous healing in various types of lesions, the influence of medical and surgical treatment on the rate and degree of healing, and the type of lesion in which spontaneous or medical treatment rarely obtain, are discussed.

It was shown that no chronic gastric ulcer should be regarded as permanently healed until symptoms and niche have been absent for at least three years. The early disappearance of the niche during, or following treatment is no criterion of healing, and a healing or healed ulcer area is a *locus minoris resistentiae*, and all that it implies.

The necropsy findings in 2,000 consecutive cases in the Clinic besides other recent pathologic investigations, give positive proof of the capacity for chronic peptic ulcer to heal spontaneously.

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## PROBLEMS IN THE DIAGNOSIS AND TREATMENT OF GASTRO-INTESTINAL DISORDERS

CHARLES S. McVICAR

**Case 1** Carcinomatous gastric ulcer.—A rancher, aged fifty-four years, registered at the Clinic September 27, 1924. His mother had died from a pelvic tumor, and one brother had died as a result of "tumor of the stomach." The patient had never consulted a doctor before, except to have a dressing for an accidental gunshot wound at the age of twenty. In the fall of 1923, he first noticed an epigastric distress when the stomach was empty. He would get relief from a glass of milk, or, if food were not available, from a soda tablet dissolved in water. Throughout the winter of 1923-1924 he was free from this distress, but it recurred in the spring, subsided somewhat during the summer, and started again in the fall, about a month before his coming to the Clinic. There had been no vomiting, no nausea, and, so far as he knew, no loss of weight. He had not had to stop work.

The physical examination, apart from marked dental sepsis, was negative. There was no abdominal tenderness. The hemoglobin was 76 per cent (Dare). The blood Wassermann reaction was negative. A test-meal revealed a total acidity of 52, free hydrochloric acid 30, and a total content of 100 c.c. Roentgenologic examination revealed a bullet just below the right diaphragm. The duodenal bulk filled normally. Repeated fluoroscopic examinations of the stomach revealed the niche of a small ulcer on the lesser curvature of the stomach.

Exploration was advised and at operation an ulcer was found on the lesser curvature and posterior wall of the stomach, about 7.5 cm. above the pylorus. It appeared to be undergoing malignant degeneration, and a partial gastrectomy was performed (Billroth No 1). The ulcer was 2.0 cm. in diameter, and histologic examination proved it to be carcinomatous.

*Comment*—The controversy regarding the possible origin of carcinoma in chronic gastric ulcer has two aspects, one concerns the statistician and the student of the science of pathology, the other the practitioner of medicine. The clinician must take the responsibility in a given case of demonstrated gastric ulcer of rejecting or advising surgery. He has almost equal difficulty and responsibility if, in the presence of a positive

history for peptic ulcer, his  $\tau$ -ray colleague is unable to demonstrate an ulcer. This is especially true when the duodenum is clearly negative.

From the clinical history it was reasonable in this case to diagnose peptic ulcer. Only by  $\tau$ -ray could it be determined whether the ulcer was in the duodenum or stomach. Had it been in the duodenum, the possibility of malignancy could have been disregarded, but since it was in the stomach, surgery was advised for two reasons (1) because malignancy could not be excluded, and (2) because skilful surgery is a satisfactory treatment for benign gastric ulcer. Undoubtedly, careful medical management has given satisfactory results in the treatment of benign gastric ulcer, but in reaching a decision as to the type of treatment in an individual case, the clinician must be governed by the evidence in that case, whether or not malignancy can be excluded. In this case the diagnosis of malignancy could be made by the gross appearance of the resected specimen.

**Case 2** Toxic manifestations occurring during the alkaline treatment of ulcer.—A merchant, aged sixty-four years, registered at the Clinic May 24, 1924. There was a somewhat elusive history of a type of indigestion suggesting peptic ulcer, over a period of twenty-eight years. During this time, there had been occasional spells of epigastric distress with a sense of constriction across the lower chest. The food relationship was not definite, although on questioning the patient remembered that comfort followed eating. For the last two years, the epigastric distress had been more insistent, and had become associated with a colicky pain in the left lower abdomen. Both types of distress were likely to come on about 10 or 11 a.m. Relief was usually secured by lying down and applying heat to the abdomen. A glass of milk did not afford relief, but the distress would disappear for an hour or so after a full meal, only to recur and disappear spontaneously several times during the afternoon. Relief often followed the evening meal for an hour or two, but the distress returned before bedtime. The application of heat enabled the patient to go to sleep, but he frequently wakened at midnight with the somewhat widely diffused lower abdominal and epigastric distress which disappeared spontaneously within an hour. A recent short trial of medical treatment for ulcer had not benefited the patient, and business worries and a family bereavement had complicated the situation.

The patient was somewhat obese, tired looking and pale, with a diffuse enlargement of the thyroid without hyperthyroidism, and marked tenderness over the sigmoid flexure of the colon, in the epigastrium and high up in the right lumbar region. There was moderate dental sepsis. The hemoglobin (Dixie) was 69 per cent. There was no occult blood in the stools. A test-

meal revealed a total acidity of 76, free hydrochloric acid 60, and a total content of 100 c.c. A roentgenologic examination revealed a marked deformity of the duodenal cap, and there was retention in the stomach of barium taken six hours before the fluoroscopic examination. Roentgenologic examination of the colon after a barium enema showed multiple diverticula without evidence of obstruction. The urine was normal. The phenolsulphonephthalein return was 20 per cent at the end of two hours, the blood urea was 28 mg for each 100 c.c. The blood-pressure was 124 systolic and 80 diastolic.

After consultation with the surgical staff, it was decided to submit the patient to intensive medical management of the duodenal ulcer, (1) because the age and debilitated appearance of the patient seemed to increase the surgical risk, and (2) to determine, if possible, the relative influence of the duodenal ulcer and the diverticula in the production of the disability. The treatment consisted of fourteen feedings daily, of 3 ounces of a milk and cream mixture, with alkaline powders midway between the feedings. These powders each contained 15 gr of calcium carbonate. To one powder, 10 gr of bicarbonate of soda was added, and to a second, 8 gr of magnesium oxide. The powders were routinely alternated, but were varied to secure a daily evacuation of the bowels. Daily aspirations were made at approximately twenty-nine minutes after one of the afternoon feedings, to determine whether the free acidity was controlled. From the first, difficulty was experienced in controlling the free acid. When the acidity was controlled, the patient was free from distress, but every day or two, more especially in the early morning hours, severe distress in the epigastrium and left lower quadrant developed. Aspirations were done regularly at midnight, and in addition powders containing 40 gr of calcium carbonate and 30 gr of sodium bicarbonate were given late at night, on the average of one powder daily. During a period of one week the average daily intake was 383 gr of calcium carbonate, 84 gr of soda bicarbonate, and 60 gr of magnesium oxide.

On the seventh day, the patient complained of a distaste for milk. He was conscious of a peculiar sweetish taste in his mouth, which he described as "coppery." There was moderate nausea, a little vomiting, and dizziness with a slight dull generalized headache. The distaste for milk caused a feeling of nausea whenever the patient looked at the container, or even thought of milk. The powders were at once discontinued. On the eighth day the urine was alkaline. The specific gravity was 1.012, there was a trace of albumin, and a few casts in the urine. The blood urea was 28 mg for each 100 c.c., the plasma chlorids were 469, and the carbon dioxide combining power of the plasma was 88 volumes per cent. After two days, the nausea, dizziness and headache had disappeared, and the appetite returned, but the abdominal distress also recurred. Therefore full treatment was resumed. Two days later, nausea, the sweetish metallic taste, occasional slight vomiting, dizziness and headache again developed, and the patient craved cold liquids, especially water. He also complained of aching in the joints. The blood urea was then found to be 121 mg for each 100 c.c. The urine was alkaline, but there were no casts, and no albumin. The specific gravity was 1.011. The phenolsulphonephthalein return was 20 per cent. The plasma chlorids

were 426, and the carbon dioxide combining power of plasma, 92 volumes per cent. Alkalies were at once discontinued, and water administered. Gastric retention was guarded against by daily aspirations, but did not become a feature since the average quantity recovered did not exceed 200 c.c. daily.

Operation was undertaken June 19, 1921, seventeen days after the commencement of the medical regimen. A chronic penetrating ulcer of the duodenum was found to involve the entire upper third, beginning about 1 cm below the pylorus, and extending down for a distance of about 2.5 cm. The ulcer had perforated on the interior surface, and had been protected by a tag of gastrohepatic omentum, the area of induration was approximately 3.5 cm in diameter. There was a great deal of localized peritonitis. A gastro-enterostomy was made. Convalescence was uneventful.

October 11, four months after operation, the patient reported that there had been no recurrence of pain, either in the epigastrium or the left lower quadrant. He had gained 13 pounds in weight, and felt well.

*Comment*—The symptomatic relief from pain in the left lower quadrant under intensive medical treatment for the duodenal lesion, and the complete disappearance of pain in this region after gastro-enterostomy suggests that pylorospasm and sigmoid spasm were interdependent, and that in all probability the diverticula demonstrated by the opaque enema were the result of repeated spasmodic contractions of the large bowel, rather than the cause of the painful spasm. The findings at operation remind us that we are unable with any accuracy to determine by the clinical or roentgenologic findings the amount of gross anatomic change in the duodenum, due to chronic ulceration. In selected cases of peptic ulcer, especially in the stomach, in which there are physical signs of painful induration, a short preoperative course of relative or absolute rest to the stomach, may bring about a very desirable reduction in the degree of inflammatory reaction in the tissues around the ulcer, and so render surgical procedures correspondingly safer.

Our main interest in this case, however, arises from the occurrence of toxic manifestations during the alkaline treatment for ulcer. Attention was first directed to this condition by Hardt and Rivers at the Mayo Clinic. The clinical characteristics as outlined in their paper, and manifested in this patient are distaste for milk, and a bad taste in the mouth, nausea, headache, dizziness and aching in the joints. Toxic symptoms are more likely to occur in patients who are resistant to treat-

ment, that is, in whom it is difficult to control the free acidity by the usual moderate administration of alkalis. Symptoms may, however, occur with such small amounts of neutralizing powders that an idiosyncrasy to these drugs seems probable in certain persons. The laboratory findings of high blood urea, high alkali reserve, and lowering of plasma chlorides are similar to those found in the toxemia of intestinal stasis, and suggest that the metabolic disharmonies are similar. It has been shown that tetany is to be anticipated when the carbon dioxid combining power of the plasma rises above 100 volumes per cent. Alkalies are therefore contraindicated in all cases in which there is a rise in alkali reserve, or should at most be used only with the utmost caution. Moreover, the effect on the carbon dioxid combining power of the plasma should be frequently determined during the treatment of patients with an idiosyncrasy to alkalies. The syndrome indicating toxicity is so characteristic that early recognition should be easy. Recovery has usually been prompt following the withdrawal of neutralizing powders. If the clinical symptoms, or blood chemistry studies, indicate a marked toxemia, the treatment outlined for the toxemia of intestinal stasis should be instituted.

**Case 3 Toxemia in acute intestinal stasis**—A housemaid, aged forty-five years, was admitted to the hospital June 20, 1924. She was markedly prostrated, dehydrated, and semicomatosc. It was impossible to get a coherent subjective history from the patient or her friends, but subsequently it was ascertained that for about one year she had had "bowel trouble," namely, progressively increasing constipation and occasional diarrhea. For two weeks previous to admission she had not had a bowel movement, during this time there was anorexia and frequent nausea, but no vomiting. On admission, the blood pressure was 100 systolic, and 75 diastolic. The whole of the large bowel was outlined by impacted feces, and digital examination of the rectum revealed a papillomatous mass on the left rectal wall. The temperature was 97°. The urine was acid and contained albumin 2, and casts 4. The specific gravity was 1.013. The ocular fundi were normal, the peripheral vessels were not thickened. The erythrocytes numbered 4,820,000, and the leukocytes 14,800.

June 21, castor oil was administered in 2-dram doses every two hours, simple enemas were repeated throughout the day, and 1 liter of physiologic salt solution was administered by hypodermoclysis. The blood urea was 250 mg for each 100 c.c. This finding, and the clinical evidence of shock, led to more complete blood chemistry studies, and to a diagnosis of toxemia.

of intestinal obstruction, when it was found that besides marked rise in the blood urea, there was a striking depletion of plasma chlorides and a tendency to a high carbon dioxide combining power of the plasma (Table 1)

TABLE 1  
THE SUBSEQUENT COURSE OF THE ACUTE STAGE OF THE  
ILLNESS

Date.	Blood urea mg.	Creatinin mg.	Plasma chlorides	Carbon dioxide	Hemoglobin (Hb) per cent	Blood pressure		Intravenous in take cc	Sodium chlorid 5 gm.	Glucose gm.	Urine output cc
						Systolic	Diastolic				
6/21/24	250	2.9		64	127	100	75	1000	10	100	
6/22/24											500
6/23/24	267	4.0	233	74	134	64	46	3000	30	300	1300
6/24/24	186	2.9	396	79	125	76	48	1500	15	150	900
6/25/24	79	1.3	388	78	114	88	56	1000	10	100	450
6/26/24	96	1.8	601	72		90	65	2000	20	200	900
6/27/24	50							2000	20	200	1050
6/28/24	31			526		100	60	1000	10	100	1500
6/30/24	23	1.3									1250
7/1/24	25	1.7									1500
7/4/24	38	1.3	575		88	90	70				

The patient was nasoenteric and had rectal incontinence, so that oral or rectal administration of fluids was impracticable. She was given intravenously a sterilized solution containing 1 per cent of sodium chloride and 10 per cent of glucose in freshly distilled water. Clinical improvement paralleled improvement in the laboratory findings. At the end of ten days the patient was taking adequate nourishment by mouth. July 7 a proctoscopic examination revealed a large area of bleeding polyposis in the left rectal wall just above the anus. July 9, an x-ray examination of the colon revealed a marked defect in the rectosigmoid with marked dilatation of the colon. July 10, a test meal showed that there was no free hydrochloric acid in fractional titrations up to two hours. Fluoroscopic examination and roentgenograms did not reveal abnormalities in the stomach or upper duo denum.

*Comment*—The clinical course and laboratory findings in this case are those of the toxemia heretofore found only in certain cases of gross disturbance of motor function of the upper gastro-intestinal tract. Interruption of motor function may be due to obstruction by malignant or inflammatory infiltrations, or to exhaustion (decompensation) of the muscle above organic lesions which only partly occlude or may follow operations such as gastro-enterostomy, when stasis occurs postoperatively, it may be due to mechanical obstruction, such as a kinking of one or both loops of the jejunum. Not infrequently, stasis appears to be due to a temporary paralysis of the muscular tube, and after a longer or shorter refractory period, function is restored.

It may be that in this case stasis was complete throughout the large and small bowel, but the cause was shown to be confined to the large bowel. It would appear that the clinical and laboratory findings characteristic of the severe toxemia of intestinal stasis may be present in the absence of vomiting, and further that the loss of hydrochloric acid by vomiting is not the cause either of the fall in blood chlorids or the rise in the alkali reserve. Vomiting when it occurs cannot, of course, be excluded as a possible factor in producing these two phenomena, but on the other hand, the absence of vomiting or of gastric retention in a suspected case of intestinal stasis should not delude the clinician into a false sense of security.

There is evidence that tetany, occurring in cases of intestinal stasis, should be considered not as a clinical entity, but rather as a possible complication of the toxemia, and that its occurrence bears a definite relationship to the carbon dioxid combining power of the plasma. Tetany may be anticipated when the carbon dioxid combining power of the plasma rises above 100 volumes per cent.

The object of treating organic obstruction is to place the patient in a safer condition for surgical procedures. In non-obstructive ileus, an effort is made to counteract the effects of the toxemia until muscle function is restored. The progress of treatment can be measured by frequent chemical examinations of the blood.

The outstanding features suggesting treatment are dehydration, diminished output of urine, low blood pressure, shock-like prostration, high nonprotein nitrogen content of the blood, low blood chlorids, and a tendency to a high carbon dioxide content of the blood. The administration of water is indicated to control dehydration, to counteract shock, to promote diuresis and to wash out nitrogenous waste products.

It is not clear whether the high blood urea is evidence of excessive tissue catabolism or of retention due to renal inadequacy, or whether both factors are involved. Glucose has been used to spare protein, and in intravenous injection to promote diuresis.

Experimental and clinical experience indicates the administration of salt. There seems to be a markedly increased demand in the tissues for sodium chlorid. In spite of a liberal intake of sodium chlorid, the output of salt in the urine may be scanty, even for several days after the blood chlorids reach a normal level. Perhaps the most important single fact which blood chemistry studies have revealed concerning this type of toxemia is the invariable tendency towards alkalosis. The administration of alkalis is, therefore, clearly contraindicated in proved or suspected cases of toxemia associated with intestinal stasis.

**Case 4** Diverticulum of the stomach.—An insurance agent, aged fifty years, registered at the Clinic September 4, 1924. His health had been good until eleven months before, when he noted a burning sensation in the mid-epigastrium and behind the lower end of the breast bone, coming on about four hours after the midday meal. This occurred daily for five days, and was relieved immediately by a half teaspoonful of bicarbonate of soda. At the end of a week, burning was noticed about one or two hours after every meal. Food would afford relief for a little while, and 30 gr of soda bicarbonate would give instant, but temporary relief. After a few days the burning sensation in the epigastrium and lower chest merged into a distinct, throbbing pain, resembling toothache. Burning and pain came every day. Acid fruits, hot liquids, and fatty foods increased the discomfort. Meat and cheese were well tolerated. The patient's appetite was good, but he was afraid to eat. He began to be awakened at 1 or 2 a.m., with epigastric pain and a desire to vomit. He often gagged, but he vomited only twice during the course of his illness. The night pain was often severe enough to cause him to get up and go for a drive or walk. Soda continued to give instant, but only temporary relief. Four months from the onset, the pain had become

increasingly severe, but remained localized and did not radiate. The distress became constant, ceasing to have any relationship to the taking of food. Soda was taken every hour, and food intake reduced. Beefsteak and cheese were tolerated best. After two months of this more severe distress, there were intervals of one or two days of complete freedom from pain. For one month previous to coming to the Clinic, the patient had eaten freely, but taken care to exclude fats and sours. His appetite was splendid, and he had had two weeks of complete freedom from distress. During the second and third months of his illness, he had followed a fairly rigid regimen for ulcer, and during this period his weight dropped from 155 to 98 pounds.

Physical examination was essentially negative. The patient was apprehensive and "nervous," but appeared well nourished. He weighed 138 pounds. Deep palpation in the epigastrium revealed a nodular tumor about 1.5 cm in diameter in the median line, midway between the umbilicus and ensiform. The hemoglobin (Dare) was 86 per cent, the erythrocytes numbered 4,960,000, and the leukocytes 8,000. The blood Wassermann reaction was negative. A test-meal revealed a total acidity of 86, free hydrochloric acid 66, and a total quantity of 100 c.c. Roentgenologic examination of the stomach revealed a circumscribed filling defect in the pyloric third of the stomach which did not encroach on either the lesser or greater curvature. A diagnosis was made of gastric tumor, probably benign, and exploration was advised.

A tumor was found on the posterior wall of the stomach, commencing about 5 cm above the pylorus, and having a base, 5 cm in diameter. A segmental resection of the tumor-bearing area of the stomach was made, a cautery being used for the incision. The defect was closed by appropriate sutures. No gastro-enterostomy was made. The excised tumor was found to be a diverticulum, 3 cm in length, rather benign fibrosarcomatous changes were starting, apparently in the submucosa.

Convalescence was uneventful, and November 10, the patient was actively engaged in his occupation.

#### DISCUSSION

The correlation of the clinical and roentgenologic evidence is of value in the preoperative diagnosis and prognosis of intrinsic gastric lesions, especially when it enables us to entertain a reasonable doubt that cancer is present. It is often possible to resect satisfactorily benign lesions of large size, even if placed relatively high in the stomach, whereas carcinomas of similar size and position would carry a doubtful prognosis. In this case, the evidences favoring a diagnosis of benign tumor and against malignancy were a gain of 40 pounds in weight, the healthy appearance of the patient, the high gastric acidity, the severity of the pain, and the circumscribed appearance of the filling defect as shown by x-ray.

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From a study of the roentgenologic findings in twenty-three cases of benign gastric tumors Moore has defined the following signs as suggestive, if not characteristic (1) they produce a filling defect that is circumscribed and punched-out in appearance, (2) the filling defect is usually on the gastric walls leaving the curvature regular and pliant, (3) the rugæ are obliterated in the immediate area of the tumor, just as in inflammatory and malignant lesions, but the rugæ surrounding a benign tumor are more nearly normal in their arrangement and distribution, (4) they cause little or no disturbance in peristalsis, and retention is uncommon except when the lesion is at, or very near, the pylorus, (5) they do not reveal a niche, nor is there any incisura or other evidence of spasm, and (6) they are rarely sufficiently large to be palpated

Nonobstructing carcinoma of the stomach rarely gives rise to severe pain. The failure of symptomatic relief on treatment, the absence of tenderness or of referred pain, the palpable tumor, taken together with the extensive x-ray defect made the diagnosis of gastric ulcer improbable

The rarity of diverticula of the stomach is indicated by the finding of only six cases from 1910 to November, 1924, during which time 4,713 operations were performed at the Mayo Clinic for intrinsic gastric lesions. Of the six resected specimens two showed malignant degeneration. In one of these the malignant change was that of colloid carcinoma. The second case is the one here reported.

# DUODENAL ULCER AN ANATOMIC STUDY

H E ROBERTSON AND ESTES H HARGIS

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## INTRODUCTION

In the evolution of any species it must be true that the reactions to environment undergo constant modifications, brought about by the inevitable changes in the constitution of the succeeding generations, and the just as certain changes in the nature of the environment. While these reactions undoubtedly follow fundamental physical laws, comparatively simple in their last analysis, the multitude of them and their intricate interrelationships furnish a complexity difficult or impossible to unravel in all details. Especially is this true of the more highly developed animals such as man, in whom we often are cognizant of changes in reactions only by recognition of the results of these reactions. We see new phenomena without always being able to estimate correctly the reasons for their appearance.

Thus it is not only possible, but even necessary, that certain diseases, the pathologic results of reactions to environment, should disappear in whole or in part, and other and new diseases just as certainly make their appearance. No other facts in the history of medicine are more soundly established, or receive less recognition than the results of the laws of the evolution of the diseases which afflict mankind.

A certain acceptance of this rule has been given, it is true, with respect to the plagues of the human race. Almost every student will admit the cyclic character of epidemics and their often evanescent course. It may even be granted that history records details of pandemics no longer known or even identifiable. But the same methods of study have rarely been applied to the systemic diseases of the body, and the majority of medical writers would appear to conclude that when they had once

established the essential data concerning any disease of any organ, this task was accomplished for all time. They fail to consider that any particular organ and its environment is constantly and permanently changing, and the disease which today follows a definite known course may, in the passage of future generations, become hardly comparable with the disease which takes its place. In short, we may readily assume that Virchow, reincarnated a hundred years from now, would find many pathologic conditions which he had never seen before, and the microscopic appearances of the various organs under varying pathologic reactions would be largely new ground for his experienced eyes.

Hence it is not only new knowledge, attained by new methods, which changes our conceptions of disease processes, the diseases themselves are changing, and in the course of time it becomes necessary to correlate the facts concerning them in order to establish, and to be able to appreciate, the extent of this change. The present study is offered to illustrate this fact, and furthermore to give deserved emphasis to certain pertinent anatomic phases of the subject.

#### ANATOMY AND PHYSIOLOGY

The first portion of the small intestine received its name "duodenum," meaning twelve, from the fact that it is about equal in length to the breadth of twelve fingers. It is the shortest, the widest and most fixed part of the small intestine, and is arranged in the form of a loop with a forward convexity, which loop might be considered as a ring suspended at an upper and a lower point. The duodenum is usually divided into four parts.

The first portion is of the most importance in relation to ulcer, and is the free and movable portion immediately below the pylorus. The three lower segments are retroperitoneal, and their curve usually corresponds to one of three types, the "U," "V," or "C." The circuitous course described by this portion of intestine presents an S-trap arrangement, the mechanics of which, according to Jonnesco allows the food and

secretions from the stomach as well as the secretions from the liver and pancreas to accumulate, and also prevents the passage of gases from the intestine into the stomach

Anatomically the first portion of the duodenum is situated on the borderline between the areas supplied by the celiac axis on the one hand, and by the superior mesenteric on the other. Both Wilkie and Reeves have thoroughly worked out the blood supply of this region, and have shown that the critical area is supplied by a variable branch, the supraduodenal artery, which is of the end-artery type with a paucity of anastomosis. There is no distinct line of arterial demarcation at the pylorus, as it is rather easy to trace branches across the pylorus in the outer and inner layers by injections and  $\gamma$ -ray. Reeves has shown microscopically that the gastric type of artery is to be found in the mucosa of the first portion of the duodenum.

The gastro-intestinal tract, in certain respects, must be considered as a unit, a coordinated mechanism, a continuous tube for the reception, digestion, absorption and elimination of substances concerned in the metabolic activities of the body. At this time, however, emphasis must be placed on the individuality or special functional activities of some of its subdivisions. Just how far this specificity applies to the duodenum has been the incentive for experimental investigation for a number of years. The duodenum occupies an important physiologic and anatomic position just distal to the stomach, and is intimately associated with the physiology of that organ, particularly with reference to its emptying. However important this normal function may be, it has been definitely shown by Mann and Nakamura that animals are able to live in an apparently normal condition for indefinite periods after complete removal of the duodenum.

That the duodenum may also be the site of perverted functions, and that these perversions may have the most profound, even fatal, effects on the body as a whole, has been shown by Whipple, Sweet, Ellis, and others. In the light of these investigations it becomes quite probable that all the physiologic conditions governing the duodenum are by no means clear.

The sharp change in the character of the mucosa and musculature at the pylorus, the peculiar shape of the organ, and the close relation between the discharge of bile and pancreatic juice on the one hand, and important digestive processes on the other, give a more distinctive character to this portion and to its processes than is usually accorded to it.

#### HISTORICAL NOTES

According to Leube, Galen mentions ulcer of the stomach, and Celsus lays down rules for its treatment. In his translation of the works of Paulus Aegneta, Adams asserts that both Rhases and Avicenna describe ulceration of the stomach very accurately.

With the more common practice of postmortem examinations this condition was occasionally noted as the cause of death. Thus, Grassius, in 1695, gives an account of a perforated gastric ulcer, and in 1704 Littré found the source of a severe fatal gastro-intestinal hemorrhage in an "ulcus rotundum," five lines broad and half a line deep. Duodenal ulcers also received casual mention, for example, by de Muralto who, in 1688, described two perforations in the duodenum of a soldier. However, Morgagni in 1728, while describing in some detail cases showing gastric ulcers and even perforation by them, barely mentions erosions of the duodenum. It is quite evident that little recognition was given to duodenal conditions, whereas other lesions including ulcers of the stomach, were well known. Indeed Matthew Baillie in his work on pathologic anatomy in 1793, devotes a special chapter to the subject of gastric ulcer (Leube) without mentioning the duodenum.

Nevertheless, about this time, Penada is said by Lenepveu to have mentioned a case of duodenal ulcer, and in 1802 Neumann described a perforation of the duodenum in a man with strangulated hernia. A second case is reported by Gerard in 1804. The ulcer was four lines below the pylorus, and resulted in a fatal peritonitis. Travers, in 1817, published data concerning two instances of perforated ulcer of the duodenum. In 1825

Broussais,\* gave the details of a further case, and others were added by Rayer in 1826, Robert in 1828, Lenepveu in 1839, Holscher, and Bainbridge in 1842. In spite of these, Cruveilhier, who gave the first clear cut anatomic differentiation of cancer and ulcer of the stomach, and defined the "ulcus ventriculi simplex," does not mention duodenal ulcer. In 1828 Abercrombie wrote, "Although we do not have any extensive observations as yet, still it is probable that the duodenum is the site of various diseases that one can easily confuse with diseases of the liver or stomach." Hence it is not surprising to find this same author reporting, in 1836, a perforating ulcer of the duodenum.

But it was not until 1839 that any statistics were collected with reference to either duodenal or gastric ulcers. Rokitansky in that year reported observations on seventy-nine peptic ulcers, six of which were in the first part of the duodenum. About the same time Andral collected ninety-two cases of gastric, and two, of duodenal ulcers.

In 1842, Curling reported in some detail twelve cases in which duodenal ulcers or inflammation had followed severe burns. This relation of ulcers to burns had first been noted by Dupuytren and was confirmed by numerous later writers, among others, Long, Erichsen and Hewett.

Mayer, in 1844, was the first to publish a monograph on the duodenum. More clinical than anatomic, his discussion includes ulcers both perforating and healing. He emphasizes burns as an etiologic factor. No comparison with gastric ulcers is given, although he regards the duodenum as a sort of second stomach. Cancer and tuberculosis have etiologic significance, but he concluded that "nothing is as yet known with respect to the diagnosis of duodenal lesions."

Bardeleben, in 1853, in reporting a case of perforated duodenum, said, "Of all parts of the intestinal canal the duodenum shows ulcers least often, as Andral had already pointed out."

\* Maret says that Broussais was the first to mention peptic ulcer of the duodenum, and several authors begin their historical review with his publication.

He agreed with Rokitansky that they resembled the ulcers found in the pylorus of the stomach. However, Virchow, in the same volume of his famous *Archives* in which Bardeleben reviewed his case, gives his views on the etiology of gastric ulcer, but makes no mention of ulcer of the duodenum, in this or any other of his writings.

In a review of the postmortem work in the Pathologic Institute at Prague, extending from February 1, 1854 to March 31, 1855, out of a total of 1,146 postmortem examinations Willigk noted gastric ulcers in 225 (forty-six men and one hundred seventy-nine women) (19.6 per cent), and duodenal ulcers in only six (three men and three women) (0.5 per cent) a proportion of 37.5 to 1.\*

It is interesting to note that Brinton, who, in 1856, wrote a very comprehensive account of ulcers of the stomach, and collected considerable literature, reviewed the results of 7,226 postmortem examinations and concluded that gastric ulcers occur in an average of about 5 per cent of all persons, dismissed "ulceration of the duodenum, which often follows severe burns" with the comment that "its situation, cause and appearances alike seem to me essentially distinct from ulcer of the stomach." In this same period appeared studies by Claus, Frank, Nick and Murchison, all of whom concerned themselves with the phenomenon of perforation in individual cases, although in 1859 Ranking, in describing a fatal case of hemorrhage from a duodenal ulcer, remarked on the comparative rarity of the presence of an isolated ulcer of the duodenum.

Müller's work in 1860, often quoted, added practically nothing to the subject of duodenal ulcers, and his data on ulcers of the stomach were hardly equal to Brinton's admirable study.

During the following decade single cases, sparsely scattered in the literature, were reported by Bouchaud, Kneeland, and Haldane in 1862, Larcher in 1864, Malherbe in 1864, Feierabend in 1866, Clark in 1867, Cuthbertson in 1867, Ebstein

\* This same author is reported by Nidergang to have analyzed 1600 postmortem examinations in 1833, and to have observed seventy-four ulcers of the stomach and only two of the duodenum, a proportion again of 37 to 1.

in 1867, Barclay in 1870, Wadham in 1871, and Chauffard in 1871 Billroth in 1867, related that when Professor Arnold of Heidelberg was performing a postmortem examination, he found a duodenal ulcer which had apparently caused no symptoms during life

Another phase of the subject was introduced by Hecker and Buhl in 1861, who reported eight cases of gastric or intestinal hemorrhage in infants, one of whom had a duodenal ulcer Spiegelberg added two similar cases in 1869, and since then studies of this subject have been given, among others, by Kundrat, and Landau in 1874, Rehn in 1875, Veit in 1881, and Helmholz in 1909

Influenced perhaps by Brinton's and Muller's admirable studies on gastric ulcers, there arose similar efforts with reference to ulcers of the duodenum One of the earliest of these was published by Klinger in 1861, who noticed ten cases in the literature and added three of his own Forster in 1861, and Falkenbach in 1863, also contributed analytic reviews

One of the most thorough of the earlier studies was made by Trier in 1864, who analyzed the postmortem records of the Frederic Hospital at Copenhagen from 1842 to 1862 In a total of 261 simple ulcers, only twenty-eight (10.9 per cent) were in the duodenum He confirmed the usual observation as to the relative frequency of gastric ulcers in women, quoting Brinton's figures of 440 women to 214 men, and compared these to his collection of fifty-four cases of duodenal ulcer, forty-five of which were in men and only nine in women He was the first to describe in detail the distortion of the duodenum, caused by the healing of ulcers

In the following year the much more widely known work of Krauss appeared He gave statistics of eighty cases noted in the literature, and is usually given credit for the first comprehensive survey of the subject Of sixty-four of his cases, fifty-eight were in men and only six in women Many recent writers on duodenal ulcer date the modern study of this subject from the time of Krauss' work In this same year a thesis by Morot gave details of twenty-two cases, eighteen in men and

four in women. He quotes Brinton as authority for the statement that duodenal ulcer is five times more common in men than in women.

Following the example of Krauss papers on duodenal ulcers appeared in rapidly increasing numbers, many of them in the form of theses by German or French students. Thus Treibmann, in 1867, reported fourteen cases. He agreed with Krauss that "vollständige Heilung ist wohl selten." Teillaus, in 1869, found sixteen cases, and discussed the various theories as to origin of the ulcers. From 384 postmortem examinations, Starcke, in 1870, discovered thirty-nine examples of simple ulcers or scars, but only three were in the duodenum.

Schulze, in 1873, in his thesis, and in a case report endeavors to show the embolic origin of duodenal ulcers.

O'Hara, in 1875, in presenting the details of the first case of perforating duodenal ulcer ever given before the Philadelphia Pathologic Society said, "But little has been written of it," and that DaCosta had said in his "Medical Diagnosis," "Were it (duodenal ulcer) more frequent, it would be a constant source of error in diagnosis." In a similar presentation before the New York Pathological Society, Loomis, in 1879, remarked, "Perforating ulcer of the duodenum is not common," and in discussion Peters added that there were only ten cases in the records of this society. Moore, in 1883, reported two cases at the Pathologic Society of London, and asserted that from 1867 to 1882 only three cases were recorded on the postmortem records of St. Bartholomew's Hospital. Similarly, Siegel, in 1877, in a dissertation from Erlangen, in which he reported twenty cases, emphasized the lack of any extensive literature on the subject, and Clark, in 1881, in his discussion in Boston, said that duodenal ulcer is a comparatively rare disease occurring in the proportion of one to thirty gastric ulcers.

Nidergang, in 1881, produced the most complete review since Krauss. He directed attention to the greater frequency of the ulcer in men than in women, the reverse being true of gastric ulcers. This same point was emphasized by Lebert in 1878, who found that of thirty-nine patients with duodenal ulcers,

thirty-one were men, and eight, women Nidergang noted only thirty-seven cases from the literature

Grunfeld, in 1882, analyzed 1,150 postmortems from Copenhagen, performed on men of more than fifty years, and women of more than sixty Scars were found in the stomach in 124 instances (11 per cent) In 578 men, scars were found in twenty-two (4 per cent), and in 632 women in 102 (16 per cent) He found them more frequently, if searched for carefully In the entire series, however, only four scars were found in the duodenum, three in men and one in a woman

Alloncle, in 1883, in a thesis reports one case, and reviews forty-four noted in the literature All but one of the patients were males

Chvostek, in 1883, noted fifty five cases in the literature since the collection of Krauss, and added eight of his own He concluded that duodenal ulcers were more common in infants than gastric ulcers, but in adults occurred once in women to eight times in men He said that complete scarring (denied by Krauss) was usually missed, because it was not searched for carefully Distention or bulging of the duodenal wall in ulcer was emphasized by Turner, in 1864 Bucquoy, in 1887, said that the ulcers are more often present on the anterior wall Krauss giving the proportion of fifteen anterior to six posterior Johnson, in 1888, gave a very able review of the literature without adding much to the subject He says that Osler, in a review of 1,000 postmortems, found only nine ulcers of the duodenum Pepper, in 1889,\* says that "all are agreed as to the rarity of duodenal ulcers it is doubtful if more than seventy authenticated cases are on record "

Le Renard, in 1891, found recorded in the literature, forty-two duodenal and 492 gastric ulcers, the former were more common in men than in women

Perhaps the most thorough and valuable review the literature affords is that of Oppenheimer, in 1891 He reaffirms the

\* This same year Mikulicz presented, before the German Congress of Surgery, a notable contribution on the surgical treatment of peritonitis from perforation

view that duodenal ulcer is much rarer than gastric ulcer, but suggests that many small or healed duodenal ulcers may be overlooked. One other very important contribution is his observation that recurrences are very frequent, and not rarely are fresh ulcers found adjacent to old scars.

Perry and Shaw in 1893, investigated the reports of 17,652 postmortems in Guy's Hospital going back to 1826 in Dr Hodgkin's "Green Inspection Books" and ending with the close of 1892. They found that in seventy cases (0.4 per cent) there were duodenal ulcers, open or healed. In cases of burns there were ulcers of the duodenum in 33 per cent and excluding these, the ulcers were found in forty-eight males and only sixteen females. They quote Brinton as affirming that gastric ulcer is twice as common in women as in men.

In an analysis by Vonwyl, of patients in the Zurich Medical Clinic from 1884 to 1892, of a total of 12,806 there were ninety-eight with gastric and only three with duodenal ulcers, the latter were all in men. Reckman, in 1893, discusses the diagnosis of duodenal ulcer as if a new clinical syndrome had been uncovered. Collin, in 1894, collected 257 cases, 205 in men and fifty-two in women. Dickinson, in 1895, says that according to the records of the duodenal ulcers in St George's Hospital of London, fourteen were in men, and three in women (one a burn), and of gastric ulcers forty-two were in women, and only twelve in men. Maret, in 1895, very thoroughly reviews the current opinions concerning etiology. After an historical review with no new facts developed Darras, in 1897, noted twenty cases in which laparotomy was done for perforation, with three recoveries. Burwinkel, in 1898, again affirms that in comparison with gastric ulcers, duodenal ulcers are observed "ziemlich selten." He quotes Berthold who analyzed the deaths noted in Chariteannalen from 1868 to 1882, and found 262 gastric to twenty duodenal ulcers. A similar review is given by Schwartz in the same year.

During the following twenty-five years we can find no article of importance on the subject of the incidence of duodenal ulcers. The reason for this state of affairs is rather difficult to com-

prehend. It may be that in this period the increasing occurrence of these ulcers directed attention chiefly to their diagnosis and treatment. One paper only appeared which gives data useful to our purpose. In 1923 Gruber and Kratzeisen gave a review of 3,000 postmortem examinations made at the Mainz Hospital; 120 gastric and sixty-four duodenal ulcers were found. They also give Gruber's statistics from Strassburg from 1906 to 1910, in which out of 4208 postmortem examinations, there were 21 per cent gastric, and 138 per cent duodenal ulcers. In

Table 1

## Cases of ulcer reported in the literature

Author	Date	Autopsies	Duodenal Ulcers	Male	Female	Gastric Ulcers	Male	Female
Willigk	1833	1000	2			74		
	1855	1140	6	3	3	225	46	179
Tris-	1864		28			233		
Krauss	1865		64	58	6			
Moret	1865		22	18	4			
Freibraum	1867		14					
Cellaia	1869		16					
Siefel	1877		20					
Lebert	1878		54	45	9			
Chavosteck	1880		66	49	17			
Oppenheimer	1881		79	56	23			
Ferthold	1882		20			262		
Gräfheld	1883	1150	4	3	1	124	22	102
Osler	1887	1000	9					
Renard	1891		42			492		
Wenwyl	1892	12600	3	3	0	98	58	40
Perry and Shaw	1893	17652	70	52	17			
Collin	1894		257	205	52			
Dickinson	1895		17	14	3	54	12	42
Grüber	1910	4208	1386			212		
	1912	4884	1567			6573		
Sommerfeld	1911	19200	1156			1776		
Goldschmidt	1914	2300	14			21		
Hart, Musa and Holzweissig	1921	3058	163			211		
			(535)			(69)		
Gruber and Kratzeisen	1923	3040	64			120		
Way's Clinic	1924	2000	237	186	51	141	105	36

Munich, from 1899 to 1912, out of 5,884 postmortems, scars and ulcers were found in the stomach in 6.57 per cent., but in the duodenum in only 1.56 per cent. These authors give figures from Hart and Musa and Holzweissig, who from 1913 to 1921 observed 211 (6.9 per cent) gastric, and 163 (5.3 per cent) duodenal, ulcers in 3,058 postmortem examinations at the Augusta Victoria Hospital in Berlin. They further assert that Sommerfeld at the German Alexander Hospital at St Petersburg, in 19200 postmortems from 1891 to 1911, found

ulcers of the stomach in 1.77 per cent, and ulcers in the duodenum in 1.15 per cent. Lastly they give figures from Goldschmidt in Frankfort who in 1913 and 1914 in 2,309 postmortems found gastric ulcers in 2.1 per cent and duodenal in 1.4 per cent. With respect to sex, these authors found a preponderance of both types of ulcer in men, more marked in the case of the duodenum. From these data one of two conclusions must be drawn. Either there was a distinct increase of the incidence of duodenal ulcers beginning about twenty-five years before, or else more accurate observation was revealing their presence. Considering how little escaped the wonderful eyes of Virchow and his well trained scholars, the former is much the more reasonable hypothesis. However, it must be granted that when the attention is focused on finding ulcers (or anything else!), they are likely to be more numerous than in the ordinary routine examinations (Table 1).

#### ANALYSIS OF CASES

The material for our own study has been taken from the records of the Mayo Clinic between the years 1920 and 1924, and consists essentially of an analysis of the protocols of 2,000 routine postmortem examinations in which a complete survey was made of the gastro-intestinal tract. Careful attention was given to evidences of ulcer, particularly gastric and duodenal, and also to the changes or type of deformity produced by the healing of duodenal ulcers. The diagnosis of ulcer was based on gross appearances, but when there was apparent postmortem digestion or any doubt as to whether ulceration was antemortem or postmortem the case was omitted. Of the 2,000 cases studied, 378 (18.9 per cent) disclosed evidence of gastric or duodenal ulcers (Table 2), 141 (37 per cent) of which were gastric and 237 (63 per cent) duodenal. Thus, in the total series of 2,000 cases, evidences of gastric ulcer were found in 7.05 per cent, and of duodenal ulcer in 11.85 per cent. In twenty-seven (7 per cent) of the 378 cases both stomach and duodenum showed evidences of ulcer.

One hundred and twelve of the gastric ulcers (79 per cent) were active, and twenty-nine (21 per cent) were healed, ninety-

Table 2

2000 Post-mortem Examinations			
Ulcers			378 (18.9 per cent)
Gastric			141 (37 per cent of ulcers)
Duodenal			237 (63 per cent of ulcers)
Both gastric and duodenal			27 - 7 per cent (378)
Ulcers in gastro-intestinal tract other than gastric or duodenal			
1. Colon			52 2.6 per cent (2000)
2. Ileum			42 2.1
3. Jejunum			20 1.0
Carcinoma of stomach			111 5.5 per cent
Gastric Ulcers (141)		Duodenal Ulcers (237)	
Average age		Average age	
Male	52 3 years	Male	48.5
Female	45.0 years	Female	51.5
Per cent (141)		Per cent (237)	
Diagnosed	42	90	38
Incidental	99	70	62
Operated	54	38	46
Escaped	67	62	54
Single	98	70	78
Multiple	43	30	22
Active	112	79	60
Healed	29	21	40

eight (70 per cent) were single and forty-three (30 per cent), were multiple. Fifty-four patients (38 per cent) had been operated on for ulcer, and eighty-seven (62 per cent) had not been operated on. 105 were males and thirty-six were females. The average age of the males was fifty-two and three-tenths years, and that of the females forty-five and six-tenths years.

Of the 237 duodenal ulcers, 143 (60 per cent) were active, and ninety-four (40 per cent) were healed, 185 (78 per cent) were single, and fifty-two (22 per cent) were multiple. One hundred nine (46 per cent) patients had been operated on for ulcer, and 128 (54 per cent) had not been operated on. One hundred eighty-six of the patients were males and fifty-one were females. The average age of the males was forty-eight and one-half years and that of the females fifty-one and one-half years.

In the 2,000 cases active ulceration was found in the colon in fifty-two (2.6 per cent), in the ileum in forty-two (2.1 per cent), and in the jejunum in twenty (1 per cent). One hundred eleven patients had cancer of the stomach.

The age at death of the patients in this series with gastric or duodenal ulcer was at first considered separately, but the difference was so slight that they were combined and charted.

as one group (Fig. 168). There were a few patients under twenty years, but these were so occasional that the charting was begun at the twentieth year. The youngest patient encountered was three days old, and the oldest ninety-three years. There is a slight decrease about the thirtieth year, and thereafter a steady rise until a marked increase occurs at forty-five years, which is very definite and out of proportion to the yearly variations previously observed in the curve. Then there is a decrease, followed by another rise, culminating at

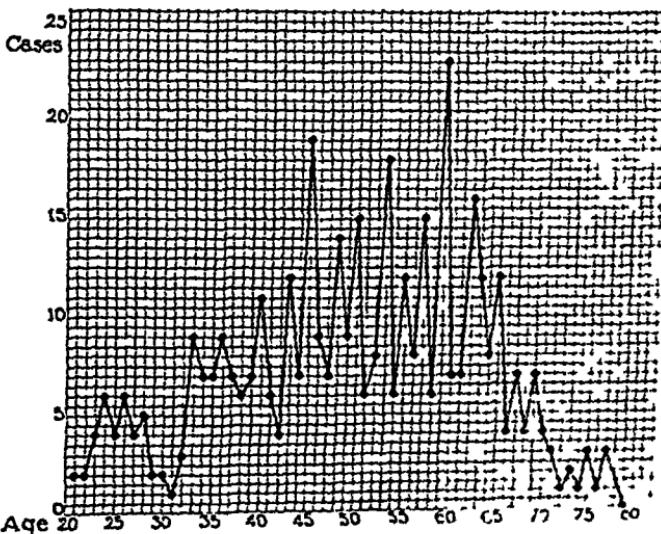


Fig. 168.—The incidence of 378 cases of gastric or duodenal ulcer arranged according to age at the time of death

fifty-eight years, after which the decrease is rapid. When the ages are grouped in five-year periods and compared with the ages for ulcer given in the United States mortality statistics for 1921, it is found that the two curves are practically identical (Fig. 169). It is interesting to note that there is a decrease in the number of ulcers found in patients dying at fifty years, compared with those dying at either forty-five or fifty-five. It should be borne in mind, in relation to these data, that the age given is the age at death, and is not to be confounded with

the age of incidence Eusterman says that the average age of the ulcer-bearing patient who comes to the Mayo Clinic to seek relief for the condition, is forty-five years, and the average duration of symptoms is nine years

The cases in which the gastric or duodenal ulcer was an incidental finding were grouped alphabetically under the chief

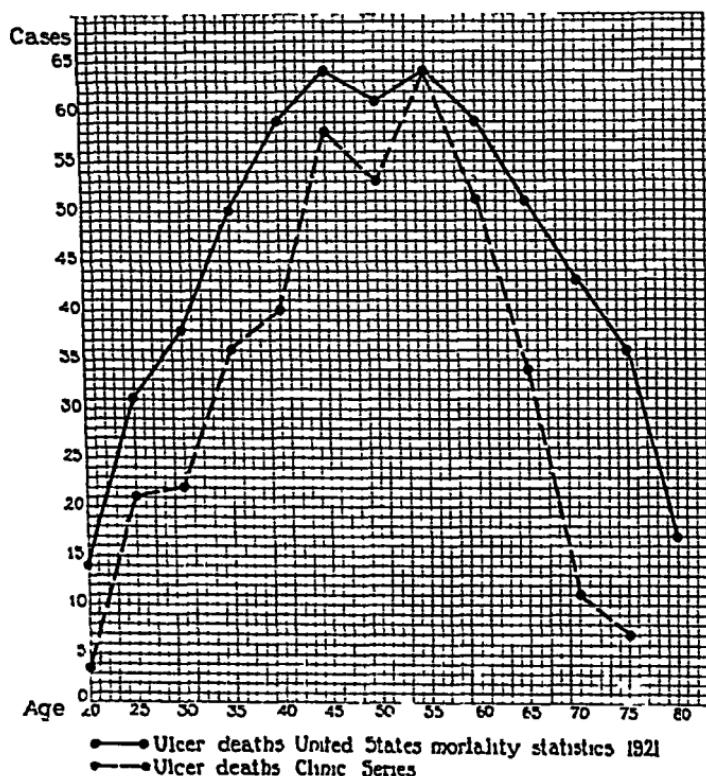


Fig 169.—The incidence of gastric or duodenal ulcers according to age at death compared with the United States Mortality Statistics

condition responsible for the death of the patient, as nephritis, appendicitis, cholecystitis, the seven conditions showing the highest number were compared. Attention has been called in the literature to the relative frequency with which gastric or duodenal ulcer is encountered in postmortem examinations of patients suffering with chronic nephritis, and the same is

true in the case of chronic cholecystitis, chronic appendicitis and the acute perforating type of duodenal ulcer found in the gastro-enteritis of infants. The finding of unusual interest in this study is the frequency with which patients dying from diseases of the thyroid, particularly toxic goiter, show evidence of gastric or duodenal ulcer (Fig. 170).

One is impressed by the fact that so many of the ulcer-bearing patients presenting themselves for treatment are harbor-

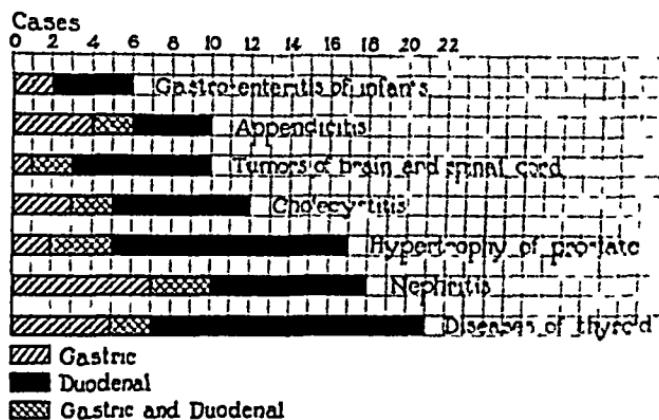


Fig. 170.—The incidence of the principal lesions associated with gastric or duodenal ulcer at the time of death.

ing definite foci of infection in the form of septic tonsils, or septic teeth showing varying degrees of periapical infection and pyorrhoea, and in other cases marked degrees of chronic prostatitis

#### ETIOLOGY

As to the etiologic factor or factors responsible for duodenal ulcer, it would be more logical for us to assume that the stomach and intestines are endowed with an inherent protective mechanism which under ordinary conditions prevents autodigestion or ulceration, but under modified conditions, which modification may be one factor or a combination of factors digestion and ulceration of varying degrees occur. Many of these ulcers heal of their own accord as is shown by the number of scars found by careful search during routine postmortem examinations.

Indeed it is quite within the range of possibility that all

of us have varying grades of ulceration of our gastro-intestinal tract repeatedly during our lives. The larger number of these ulcers give few or no symptoms, and heal of their own accord but if ulceration occurs and conditions are unfavorable for healing, it may go on to perforation or hemorrhage, or the process may be gradual and the meager attempts toward repair may be successful only to the extent of placing the ulcer in the chronic class with thick indurated walls. The lack of healing may be due to (1) poor blood supply previously existing, or brought about by the extent of the condition itself (2) generalized loss of resistance of the patient (3) constant repetition of the offending agent or (4) a combination of any of the above factors.

To obtain the normal or average measurements of the duodenum careful records were made of 100 duodenums. The stomach and duodenum were removed *in toto* with the pancreas attached, opened anteriorly from the cardia to the end of the duodenum, and the distance measured from the pylorus to the papilla. Then the pancreas was dissected free, the duodenum spread out, and five routine measurements taken. The average of these was obtained and a drawing constructed from scale (Fig. 171). The average width at the pylorus was 3.9 cm., width at papilla 9.6 cm., width at duodenoejunal juncture 7 cm., distance from pylorus to papilla 7.9 cm., and the total length 23.4 cm.

More than 95 per cent of duodenal ulcers occur within the first 3 cm. of the duodenum, it is indeed rare to find a duodenal ulcer at or near the papilla of Vater, while with congenital diverticula the reverse is true. The majority of congenital diverticula occur near the entrance of the papilla of Vater, and it is an uncommon occurrence to find one of this type in the first 3 cm. while it is common to find pouching of the first part due to the contraction and puckering of the gut, as a result of the healing of chronic ulcer. These pouchings have erroneously been called diverticula. In the healing of chronic duodenal ulcer the measurement which suffers most is the distance from pylorus to papilla.

The contraction in the longitudinal direction is fortunately, much greater than in the transverse, because if this were not the case, there would be more obstruction produced in this

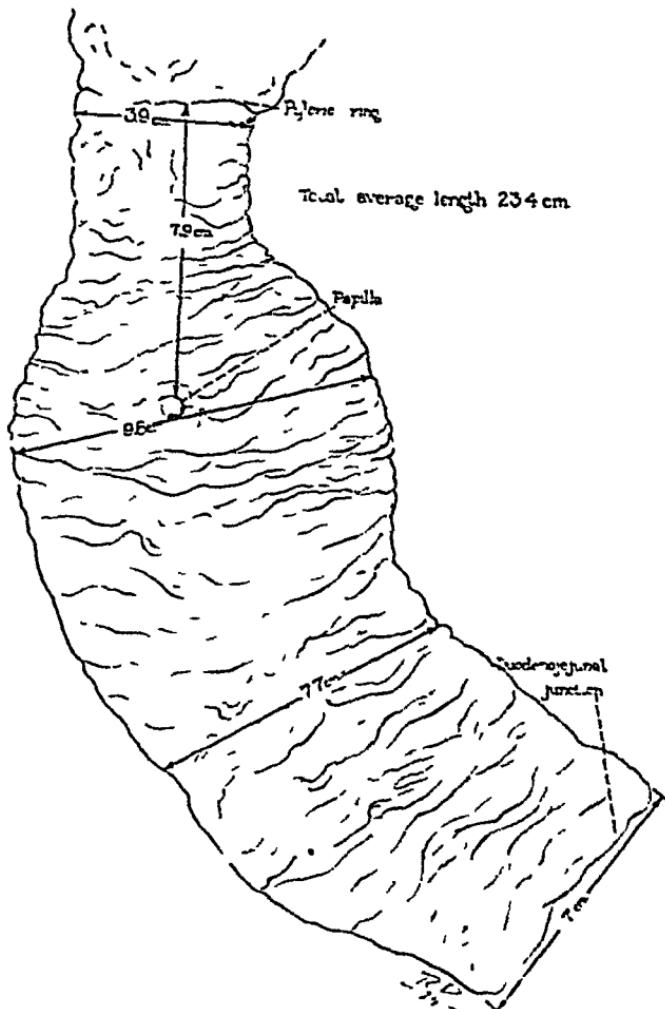


Fig. 171.—The average dimensions of the normal duodenum. Note the length from the pylorus to the papilla, usually shortened with chronic ulcer

type of lesion. It is not uncommon to find the normal distance of 7.9 cm reduced to 6 or 6.5 cm in duodenums in which old ulcers are present, or have become healed.

## DISCUSSION

The investigation both of the literature and of actual cases would seem to indicate clearly that the incidence of duodenal ulcer has been gradually, but steadily increasing. This increase has been absolute, and also relative, compared with the incidence of gastric ulcer. The remarkable preponderance of duodenal ulcers in men, as well as the increasing preponderance of gastric ulcer in men, is also worthy of mention.

The ultimate aim of the science of medicine is most concerned with the cause, and thus the prevention of any given disease, but unfortunately this study can throw little, if any, light on the etiology of duodenal ulcer. It would appear at first glance that certain fundamental changes in composition, choice, preparation or manner of ingestion of food materials, would prove to be the most plausible explanation for the noted increase in incidence, and furthermore, that if the exact nature and extent of these changes could be appreciated, the occurrence of duodenal ulcers might be prevented on the sole basis of a change in diet. While not denying the theoretic possibility of the importance of changes in dietary management, we must insist that other factors much more likely to dominate the situation must receive serious consideration. That the chemical and mechanical effects of the acid gastric chyme are of paramount importance is quite universally agreed. By substituting jejunum for duodenum in dogs, Mann has seen occur, with almost uniform regularity, postpyloric ulcers of the chronic type. In these experiments, the neutralizing influence of the fluids naturally present in the duodenum has been removed, and slight operative trauma is present. How are such effects brought about in the unoperated duodenum of man? Is it by the use and abuse of cathartics? Or, as Virchow and others have claimed, is it by vascular changes such as hemorrhages, thrombosis, embolism or arteriosclerosis? Or, as Rosenow believes his experiments show, is it by a specific infection acting in the inverse ratio to its complement specific resistance?

The correct answer to these questions has proved to be particularly difficult, perhaps largely because there enters into

portion of the stomach are brought into firm anatomic union with it. As a further complication the excessive connective tissue often formed on the outer surface of the duodenum opposite the ulcer becomes attached to the pancreas, gastrohepatic omentum and capsule of the liver, thus exaggerating the deformities already indicated. Lastly there is the anatomic narrowing of the lumen of the pyloric ring. Such narrowing is indepen-

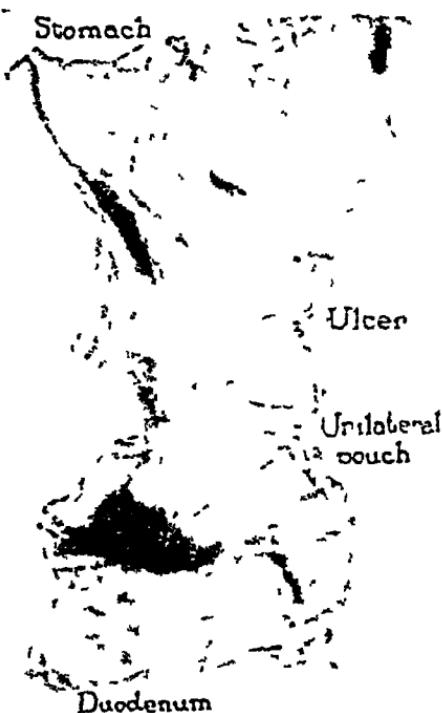


Fig. 173.—Healed ulcer of the duodenum with unilateral pouching

dent of any spastic phenomena, and is produced when the margin of the ulcer encroaches on the musculature of the sphincter. The narrowing may be marked, such that a pencil can barely pass through the opening, but more often there is simply a moderate limitation of the usual possibility of pyloric patency. Combined with spasm, this may constitute a formidable derangement.

when one considers the lack of definite proof for such a state, certainly no such proof as exists for the theory of duodenal intoxication from obstruction. However, study of the lesions seen in chronic duodenal ulcers, together with the occasional failures of relief by gastro-enterostomy and the syndrome of many of these patients, furnishes considerable grounds for the belief that in many such patients an undue stasis of duodenal contents is present, and that this stasis brings about acute or chronic, low or high-grade, attacks of intoxication quite comparable in kind, if not in degree with those caused by actual paralytic or organic obstruction.

#### SUMMARY

1 The history of the incidence of duodenal ulcer as revealed by medical literature shows a distinct rise in the last quarter century.

2 Healed duodenal ulcers are much more common than usually indicated.

3 Chronic duodenal ulcers, active or healed, bring about distortion of the duodenum, resulting in shortening, pouching, displacement and immobility.

4 These factors may cause duodenal stasis and a resulting intoxication.

5 Early recognition of a duodenal ulcer will aid future prevention.

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the problem the almost wholly unconsidered element of biologic variation of species, bringing about those changes of inherited characters which are inevitably moving the human animal toward an unknown realm of physical and mental acquirements and susceptibilities

But, after all, it is with the fact of the increasing presence and effects of duodenal ulcers that we must be chiefly concerned. Also the occurrence of small, superficial, rapidly healing and almost nonsymptomatic ulcers is to be emphasized. If they are severe enough, a scar and some deformity will be their legacy. Many probably come and go without definite clinical or anatomic signs. But when the signs of their presence present themselves, nature's danger signal is being displayed, and the smaller and the less insignificant lesion modern diagnostic methods can detect, the more proportionate benefit may accrue to the patient. Much evidence in the form of clinical recurrences as well as anatomic signs of multiplicity and scars of varying ages, give grounds for the diagnosis, in such patients, of an ulcer susceptibility, no matter what cause for this may finally be determined. So-called medical management of such cases has given such encouraging results that there is every advantage in early recognition of tendencies to duodenal ulcer and the early institution of remedial measures for its relief and, what is more important, protection from future recurring attacks.

Finally, there is another very important aspect of the problem which has not received proper attention. We refer to the subject of duodenal stasis. The deformities and alterations in the bowel produced by chronic ulcers have been noted. We know altogether too little about the physiology of the duodenum, particularly with reference to its peristalsis, however, we do know that not only is that particular function easily disturbed, but also that these disturbances lead to far-reaching and occasionally fatal results. The medical world is quite familiar with the ordinary causes and effects of duodenal obstruction. What it is not so willing to recognize are the causes and effects of duodenal stasis. The reason for this is readily appreciated.

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## CERTAIN DISTINCT TYPES OF RENAL DISEASE

NORMAN M. KEITH

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The classification of different types of nephritis is difficult, chiefly for two reasons (1) because our knowledge as to etiology of certain types is so meager, and (2) because the pathologic structure in others is not clearly defined. On the other hand there are certain distinct types of nephritis which can be recognized both clinically and pathologically. I wish here to describe the clinical course of four cases of renal disease, each case being a typical example of a definite type. The classification followed has been that of Volhard and Fahr which though incomplete, is undoubtedly the most satisfactory known at the present time.

### ACUTE GLOMERULONEPHRITIS

Until the Great War the most distinct type of acute glomerulonephritis was that occurring during the course of scarlet fever. These cases were rare, and not often seen in everyday practice, owing to their segregation by the boards of health. So-called "trench nephritis" was common among the troops of the various armies in the late war and was undoubtedly of the acute glomerular type. The clinical and pathologic features were distinct, and afford the best example of this type of renal disease. Patients were seen early and could be observed carefully for weeks and months. At the onset edema, oliguria, and uremic manifestations were common and yet the mortality was low, the maximal being 3 per cent. In many cases complete recovery occurred within from four to twelve months. Close observers believed that there was undoubtedly good healing of the original disease process as all evidence of the disease often disappeared and there were no signs of acute or chronic nephritis for months or years afterward. Case 1 exemplifies this type of nephritis.

The important therapeutic measures carried out in these cases were (1) restriction of the diet\*, (2) keeping the patient warm in bed, (3) a daily warm sponge bath, (4) the use of morphia and phlebotomy for uremic phenomena, (5) in severe cases occurring in pregnancy, premature delivery of the child, and (6) the appropriate use of ammonium chloride in cases of resistant edema. It was found that 10 gm of ammonium chloride daily was an adequate dose.

### CHRONIC GLOMERULONEPHRITIS

During the development and course of chronic glomerulonephritis certain extrarenal lesions and disturbances of general metabolism occur. The renal lesion is an important, but single item in the toxic process. Actual lesions in the heart and vascular system may give rise to secondary symptoms more serious, at least temporarily, than those due to renal insufficiency. Changes in the peripheral vessels are intimately associated with the retinal lesions so characteristic of chronic diffuse glomerulonephritis. Brown and others have also pointed out significant changes in the skin-fold capillaries. Progressive secondary anemia, altered nitrogen metabolism, and changes in the distribution of water throughout the organism constitute the important metabolic disturbances. The reaction of patients to intercurrent and focal infection is also an important factor in the course of the disease. Case 3 illustrates many typical features of chronic glomerulonephritis and is unique in that the patient was under accurate medical supervision for the entire period of the disease seven and one half years.

**Case 3**—The patient, aged twenty-four years, had always been well until the onset of the present illness in November, 1914, except that he had been subject to colds since a boy. He had first noticed slight edema around the buttocks, and a week or two later swelling of the feet and legs. Since then the edema had increased and shortness of breath developed. Six weeks after the edema was noticed he caught cold and had a headache, sore throat, discharge from the nose, and marked edema. He was in the hospital for six weeks and was found to have general anemia, and some fluid

\* The routine diet consisted of 1,500 calories, 40 gm protein, salt poor, 10 gm chloride and 600 to 800 c.c. fluid.

in the chest with a few scattered moist râles. The heart was not enlarged, but there was a systolic murmur at the base. There were signs of ascites in the abdomen, marked puffiness of the face, and marked edema of the extremities. In the urine were albumin, casts, erythrocytes, and leukocytes. The phenolsulphonephthalein excretion was 25 per cent in two hours. The eye-grounds were negative for any visible lesion.

The patient gradually improved during the six weeks' stay in the hospital. There was little change in the urinary findings, except that the phenolsulphonephthalein excretion rose to 35 per cent in two hours. He was up and about, but during the next year his ankles swelled occasionally. He was in the hospital for two weeks one year after his first admission. At this time the systolic blood pressure was 120, and the diastolic 80. The edema disappeared in two weeks. The phenolsulphonephthalein excretion was 31 per cent. The blood urea was 42 mg., and once as low as 27 mg.

In December, 1917, the patient was excluded from the air service because of albumin in the urine. Three and one-half years after the onset he still had edema of the legs. The systolic blood pressure was 140, diastolic 95. He was put to bed, whereupon the edema disappeared and the general condition improved. Five and one-half years after the onset, the systolic blood pressure was 185, and the diastolic 125, and there was occasional edema of the extremities. Soon after this he began to have periodic headaches associated with nausea and vomiting. These attacks came on after a cold in the head. November 3, 1920, six years after the onset, he entered the Mayo Clinic. Physical examination revealed definite secondary anemia, a waxy complexion, moderate enlargement of the heart with a systolic murmur over the base and apex, regular action of the heart, clear lungs, slight edema of the lower legs, systolic blood pressure 190, diastolic 120. The ocular fundi showed slight evidence of hypertension in the retinal vessels and one small hemorrhage in the right fundus, no exudates were seen. The blood count disclosed a secondary anemia, hemoglobin 42 per cent (Dare), and erythrocytes 2,300,000. The urine contained albumin, numerous casts, erythrocytes, and leukocytes. Analysis of the blood gave urea 110 mg., creatinin 6.8 mg., and uric acid 6.2 mg., and a carbon dioxid combining power of 46 per cent. A diagnosis of chronic glomerulonephritis was made.

While in the hospital the patient was found to have infected tonsils, and they were removed. In spite of a severe local reaction in the throat and a rise of the blood urea and creatinin to 184 and 16.2 mg., the patient gradually recovered from the operation and subjectively received great benefit from it. The anemia, however, continued unchanged although transfusions were given. There was also a small amount of residual edema, in spite of a rigid diet containing little salt, and a low fluid intake. The patient died in June, 1922, seven and a half years after the onset of the illness, and eighteen months after tonsillectomy.

*Comment*—An acute or subacute onset without recovery is often the early history of this type of nephritis. The association of infection of the upper respiratory tract with exacerbations

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*Comment.*—An acute or subacute onset without recovery is often the early history of this type of nephritis. The association of infection of the upper respiratory tract with exacerbations

of the disease is frequently observed. This association was so noticeable in Case 3 that, on intensive investigation, a definite focus was found in the tonsils. Whether such a chronic focus had existed throughout the disease, or had resulted from the patient's generally lowered resistance is difficult to determine. However, the removal of the tonsils was undoubtedly beneficial, in spite of a marked increase in the nitrogen retention in the blood immediately afterward, as the renal function and the patient's general condition subsequently showed marked improvement. This case teaches us that early investigation and prompt removal of infectious foci, if present, are of primary importance in the treatment of chronic glomerulonephritis.

#### CHRONIC NEPHROSIS

The outstanding feature of this group of cases is the presence of persistent edema. Patients may have definite, visible edema for months and even years, associated with marked albuminuria. The absence of cardiovascular phenomena, such as blood pressure and retinal changes, the absence of anemia, of nitrogen retention in the blood, and absence of a delayed phenosulphonephthalein excretion distinguish these cases from those of chronic glomerulonephritis. This type of renal disease was termed chronic parenchymatous nephritis by the older clinicians. The disturbance of renal function is chiefly limited to the marked albuminuria, and the faulty excretion of salts and water. There is considerable evidence of a disturbance of metabolism and the presence of edema may not only be due to inability of the kidney to eliminate fluid, but also to chemical pathologic changes in the various body tissues. The studies of Fischer, and Epstein particularly, stress these cellular metabolic changes as playing an important part in the causation of nephritic edema. Case 4 is of interest because of its known long duration with little associated general disability.

*Case 4*—A woman, aged twenty-one years, came to the Mayo Clinic February 18, 1924, because of generalized edema. Except for tonsillitis, she had had no illnesses other than the edema, which had begun after an

attack of diphtheria seven years before, accompanied by trouble with the vision and the urinary findings of acute nephritis. Since then, albumin had been present in the urine, the edema had subsided, but returned a number of times, to subside again with diet, rest and sweating. The edema, on admission, was greater than on previous occasions and had been present for several weeks.

The patient's face was puffy around the eyes, and the skin of the whole body was edematous, especially on the lower part of the legs, over the sacrum, on the inner surface of the thighs, and the anterior wall of the chest. There was no evidence of fluid in any of the serous cavities. The weight was 77.7 kg., in health it had been 71.8 kg. The eye-grounds were normal, the tonsils were large and septic in appearance, and the heart was enlarged to the left. The systolic blood pressure was 140 and the diastolic 110. The urine contained albumin 4, numerous casts, and a few pus cells, but no erythrocytes, the specific gravity was 1.027. The hemoglobin (Dare) was 76 per cent, the erythrocytes numbered 4,600,000, and the leukocytes 7,500, the blood urea was 16 mg., and the blood creatinin 1.2 mg. for each 100 c.c. A diagnosis was made of chronic nephrosis.

The second day in the hospital, the patient was placed on a weighed diet of 1,500 calories, containing 40 gm of protein, 800 c.c. of water, and very little salt. She was allowed an additional 600 c.c. of fluid, and was kept on this diet for four days as a control, during which time she lost 3.1 kg., and the output of urine rose rapidly, then diminished until, on the fourth day, it amounted to only 550 c.c. She was then given 10 gm of calcium chloride for four days. There was a sustained diuresis with a loss of 4.1 kg. in weight, which brought her weight down to 69 kg., and freed her from edema, save for a slight pitting over the lower end of the tibias. At this time, the two-hour phenolsulphonephthalein return was 75 per cent and the renal function normal except for albumin and casts. Tonsillectomy was then performed. A letter from the patient three months after dismissal stated that there was no edema, and that her weight was 68.2 kg.

The patient was again admitted to the Clinic September 27, 1924. She had remained well until August (five months after dismissal) when edema was again noted. She had continued to gain in weight until her return. Some of the increase in weight she attributed to inability to keep strictly to a low salt and low fluid diet. On admission her weight was 74 kg., her heart was slightly enlarged, her systolic blood pressure was 104, diastolic 80, the ocular fundi were normal, hemoglobin was 77 (Dare), the erythrocytes numbered 4,800,000, the urine contained albumin 3, and the phenolsulphonephthalein excretion was 75 per cent in two hours. The blood urea was 14 mg., blood creatinin 1.5 mg., and the carbon dioxide combining power of the plasma 60 per cent. The clinical and laboratory findings were almost identical with those of her previous examination. As on that occasion the patient was given a weighed diet, poor in salts and fluids, and in six days she lost 6 kg. She was then given 10 gm of ammonium chloride daily for five days, and lost an additional 5 kg., reducing her weight to 65 kg. She was dismissed October 15 in good condition, and practically free from edema.

*Comment*—The striking therapeutic response to salt and water restriction in this case is a brief for the thorough trial of such dietary treatment. The rapid development of a spontaneous diuresis on both occasions after the patient submitted to this diet also raises the question whether there might not be some specific diuretic substance in the diet itself. The beneficial results following the use of calcium chlorid during the patient's first period of hospital treatment, and following the ingestion of ammonium chlorid during the second period emphasize the practical importance of such salts in the treatment of nephritic edema. The daily use of ammonium chlorid in doses of 10 gm has proved satisfactory in this and several other cases. I believe, therefore, that it can be substituted for calcium chlorid which has a bitter taste and cannot be tolerated by certain patients. There is no doubt but that the use of calcium and ammonium chlorid, as advocated by Shultz, Blum and Haldane, has rendered certain patients with nephrosis edema-free, who otherwise would have continued to be markedly edematous. Whether these patients need or can tolerate a small daily dose of ammonium chlorid for an extended period will be determined by experience. The patient in Case 4 is now taking small doses of ammonium chlorid daily during alternate periods of two weeks. It will be of interest to note whether such treatment, with the dietary restrictions, will prevent the periodic recurrence of the edema. Renal decapsulation, particularly in the early stage of subacute nephrosis, would seem to be a rational procedure, improvement in certain cases following this operation has recently been reported by Fowler and Kidd. Double decapsulation in a case of chronic nephrosis was performed in 1921 at the Mayo Clinic. There was definite temporary improvement, with loss of edema, but subsequently the edema recurred and the patient's further course seemed to have been little influenced by this procedure.

#### DISCUSSION

The problem of the etiology in nephritis is still far from solved. Recognition of distinct types of a disease is an im-

portant step in the study of any pathologic condition. The wide occurrence of acute glomerulonephritis during the late war has given us a broader viewpoint as to possible recovery, and to the factors involved in the development of chronic glomerulonephritis. The clinical similarity between certain cases of toxemia occurring in pregnancy and acute glomerulonephritis should stimulate further investigation as to their possible common etiology. The better definition of chronic nephrosis has already led to new conceptions in the problem of edema, and to important new therapeutic procedures such as the use of calcium and ammonium chloride. The recognition of the significance of infectious foci in chronic glomerulonephritis has led to beneficial treatment.



## PYELONEPHRITIS TREATED WITH MERCUROCHROME

HERMON C. BUMFUS, JR.

A woman, aged thirty years, first came to the Clinic August 6, 1920. Her physician wrote that she had suffered for six or seven years from bladder trouble, manifested by frequent and painful micturition, the capacity of the bladder seeming to be limited to about 2 ounces. Eighteen months before the patient came to the Clinic, the right ovary and tube, and the appendix had been removed in the hope of relieving the condition in the bladder, which was thought to be the result of extravesical pressure. No relief being obtained, hysterectomy was suggested. The patient was urinating every five minutes, and intervals of more than one hour were unknown.

Physical examination was negative save for a rather marked suprapubic tenderness. Approximately fifty pus cells to the microscopic field were found in the urine, but many stained specimens failed to show the tuberculosis bacilli. A test of renal function revealed a normal return of phenolsulphonephthalein, roentgenograms of the urinary tract were negative.

Cystoscopic examination revealed subacute areal cystitis. Pus cells and colon bacilli were found in urine obtained from the kidneys. Roentgenograms revealed five devitalized teeth and one infected root. Three of the devitalized teeth had definite areas of rarefaction in the apical region, two had none. Believing that the periapical infection of the teeth might be the source of infection from which the pyelonephritis originated and was kept active, the teeth were removed surgically, and from each tooth, pure cultures of green-producing streptococci were isolated. Six rabbits were injected with cultures of these organisms and all developed marked lesions in the kidneys, from which the streptococcus was recovered. Eight other

rabbits were injected with these organisms, and in all but one, lesions in the kidneys resulted. Cultures were made at necropsy from the kidneys, urine, bile, liver, blood, and joint fluids of the animals, whether or not lesions were present. In all the animals, the streptococci were recovered from the kidneys and urine. In ten of the animals, all other cultures were negative. A culture made from a catheterized specimen of the patient's urine early in the investigation showed only Gram-negative bacilli. These were injected into two rabbits, one intravenously and the other into the bladder. Neither developed lesions of the urinary tract. Following the removal of the badly infected root the patient experienced a severe febrile reaction, and green-producing streptococci appeared in the urine in large numbers, which still contained Gram-negative bacilli. The mixed cultures from the urine were injected into two rabbits. Both animals had lesions in the kidneys, and one had a hemorrhagic lesion in the bladder. Cultures from the lesions revealed the streptococcus in both animals.

The bacteriologic findings seemed to indicate clearly that the urinary infection was initiated by streptococci from the teeth, which had a selective affinity for the urinary tract and that the colon bacillus in the urine at the first examination and believed to be the cause, was of secondary importance. Therefore all further local treatment of the bladder and kidneys was discontinued and attention directed to the removal of all devitalized teeth and the elimination of other possible foci of infection.

The patient returned home and subsequent inquiry revealed the rather disappointing fact that she had derived but little benefit from the eradication of the foci. Four years later, August 26, 1924, she returned to the Clinic complaining of great urinary frequency. An hour was the limit of urinary retention during the day, and at night she voided from eight to ten times.

Cystoscopic examination revealed a urinary infection differing but little from that of four years before. There was mild per-mural cystitis, but the irritability of the bladder

extreme, the cystoscopic examination was most painful Urine containing pus was obtained from both kidneys and on culture many colonies of colon bacilli were grown

Evidently the removal of the original focus of the disease had not interfered with its continuation in the urinary tract The renal pelvis were lavaged with silver nitrate several times, but without relief The organisms causing the symptoms, being located deep in the tissues of the bladder ureters and kidneys, were not reached by this method Only some germicide conveyable through the blood stream would, under these circumstances, be effective The disease, if once checked by such a germicide, should not recur, as its original focus had been removed. With this idea in mind the patient was sent to the hospital and 20 c.c. of a 1 per cent solution of mercurochrome given intravenously The patient experienced a trying reaction characterized by nausea and followed by a rather brisk diarrhea for several hours There was no rise in temperature. It has been my experience if the patient's temperature is normal at the time of the administration of mercurochrome that a febrile reaction either does not occur or is very slight, but if the patient has one or two degrees of fever at the time the mercurochrome is given, the temperature rises very rapidly to 104° or 105° and a chill follows, after which there is an immediate and rapid drop of the temperature to normal where it usually remains This sharp and often alarming rise of temperature may be due to the large amount of bacterial protein thrown into the blood stream as a result of the death of the organisms

Forty-eight hours after the first treatment, a second dose was administered Originally 5 mg or more of the drug for each kilogram of body weight was employed This caused nausea and vomiting almost immediately after its administration, such a dose is probably close to the margin of safety Therefore, 4 mg for each kilogram is preferred, for the average patient 20 c.c. of a 1 per cent solution is approximately this amount However, the dosage for heavier patients must be larger, as fractional doses are ineffectual from the bacteriologic

point of view. Following the second treatment, the patient experienced a rather severe chill and became salivated. Sodium bicarbonate was administered by mouth, and afforded considerable relief. As mercurochrome is soon excreted and probably produces its maximal effect within twenty minutes, the early administration of alkalis tends to minimize the unpleasant sequelæ, such as salivation and diarrhea, and does not affect the efficacy of the drug.

The night following the first administration the patient voided but twice, as eight to ten times had been the invariable rule for several years the patient and the attending physician were much surprised at the suddenness of the decrease of the irritability of the bladder, and all wondered if it would prove to be permanent. A week after the first administration, the third dose was given, and after forty-eight hours a fourth.

A cystoscopic examination made immediately after the patient left the hospital showed the cystitis to be much diminished. Urine from both kidneys was not only free from pus, but was sterile, as was also a catheterized specimen from the bladder.

Equally remarkable was the clinical improvement. The patient after finding that she could sit through a full motion picture program without discomfort, from feminine curiosity tried to see how long she could wait comfortably before voiding. The urine was retained for six hours without discomfort.

An extract from a letter received two months after the date of the first administration of mercurochrome is as follows: "I got home the morning of October 23, and went to work at noon the same day. I am feeling fine and my trouble is over. I am gaining every day."

Naturally such gratifying results are not obtained in all cases, but that mercurochrome is the most potent drug now available for intravenous use in cases of resistant infections of the kidney or bladder seems beyond denial. Its preparation and administration are simple. A 1 per cent solution is made by adding the crystals to sterile distilled water, and is allowed to stand two hours to insure self-sterilization. It is administered

with a 20 c.c. syringe, directly into the vein. Care must be taken to insure its intravenous administration, for sloughs follow any subcutaneous infiltration.

Symptoms of acidosis have occasionally developed, and the drug should, therefore, probably not be given if the renal function is much impaired. The immediate administration of sodium bicarbonate, either intravenously or orally, has always produced the desired neutralizing effect in such cases.



## DIFFERENTIAL DIAGNOSIS IN DISEASES OF THE URINARY TRACT

WILLIAM F. BRAASCH

In the diagnosis of abdominal tumors we are constantly meeting with confused clinical data which demand careful differentiation. Abdominal palpation as a means of determining the identity of a tumor is frequently misleading. What is apparently an intrarenal tumor on palpation, may prove at operation to be an extrarenal tumor, and vice versa.

### DISCUSSION OF ILLUSTRATIVE CASES

**Case 1** Tuberculous pyonephrosis.—A woman, aged fifty-three years, came to the Clinic because of frequency, dysuria and hematuria of five years' duration. This had, at first, been intermittent and of variable degree. Last spring she had chills and fever, became weak, and took to bed. At the end of the summer she was cystoscoped elsewhere, and was told that both kidneys were diseased, presumably polycystic, and that operation was impossible.

On physical examination tumors could be palpated in both renal areas. With a mass in both kidneys, and a history of hematuria, the natural inference would be that the previous diagnosis of bilateral renal involvement was correct, and that the condition was probably bilateral polycystic kidneys. Bilateral hypernephroma, simple cyst and hydronephrosis occur so rarely that they are almost excluded, and bilateral tumors are palpable in most cases of polycystic kidney. A roentgenogram of the urinary tract showed the outline of both kidneys to be almost twice the normal size, which was regarded as being corroborative of the diagnosis.

*Comment*.—In the diagnosis of renal polycystic disease the general physical examination is of the greatest importance. The clinical data are usually those of interstitial nephritis. If there is evidence of renal insufficiency in a comparatively young adult, with increased blood pressure, low urinary specific gravity, low phenolsulphonephthalein return, and high blood urea, in the presence of bilateral tumor in the renal area, the

condition can usually be regarded with certainty as polycystic kidney.

However, in this case the patient's blood pressure was 110 systolic and 70 diastolic. The specific gravity of the urine was 1.018 to 1.023, phenolsulphonephthalein return 50 per cent, and blood urea 15 mg. I have never seen a patient with polycystic kidneys, who was over fifty years of age, with such normal findings. On cystoscopic examination, considerable cystitis was present, and a large amount of pus was found in the catheterized urine from the left kidney, the urine from the right kidney was normal. The differential functional test, using indigo-carmine, showed a dark blue color on the right side, and no return of dye on the left. In order to exclude polycystic kidneys definitely, a pyelogram of the right kidney was made, and a normal pelvis found. A diagnosis was made of left pyonephrosis with tuberculosis (90 per cent probability). At operation a left tuberculous pyonephrosis was removed, and the right kidney was found to be low-lying and enlarged, evidently as the result of hypertrophy, otherwise it was normal. The mass, which was palpable in the right abdomen, and which gave the large renal shadow, was caused by the hypertrophied, low-lying kidney.

In the differential diagnosis, it should be borne in mind that if there is no positive evidence of renal insufficiency, polycystic kidney can usually be excluded. In its early stages, and in the young adult, the condition is discovered largely by accident, and there may be but few clinical indications of nephritis. In Case 1, it was largely by exclusion that a diagnosis of tuberculous pyonephrosis was made, since there was no evidence of stone or hydronephrosis. The fact that there were no *Bacilli tuberculosis* in the urine did not exclude tuberculosis, since acid-fast bacilli are not usually found in cases in which the disease is so far advanced. There is no such thing as a clinical entity of pyonephrosis, *per se*, pyonephrosis is always secondary to some other process, such as lithiasis, tuberculosis or infected hydronephrosis.

Too much diagnostic value is being placed on the interpreta-

tion of the renal outline as observed in the roentgenogram. It is very difficult to be accurate in the interpretation of this outline, extrarenal organs may give the impression that it is abnormally large or small. I have seen the apparent outline of a normal kidney when in reality the kidney had been removed at operation. Furthermore, there may be several causes for renal enlargement, such as any of the various forms of tumor, a temporary congestion, and some forms of chronic nephritis,

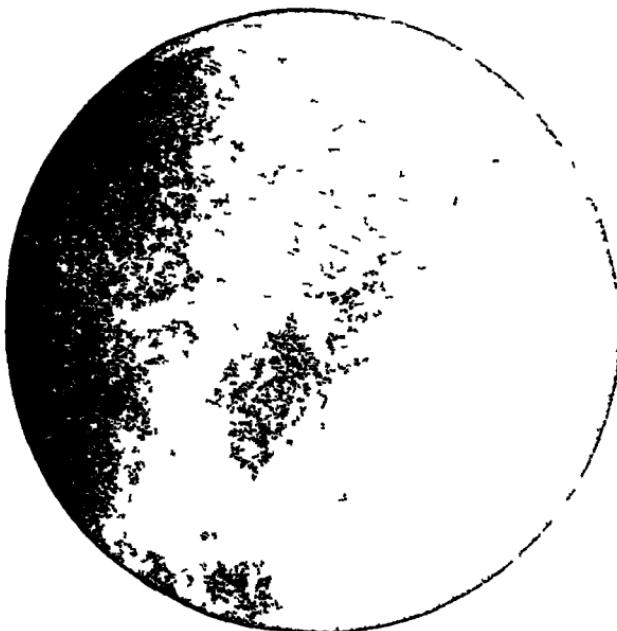


Fig. 174.—Polycystic Kidney

perinephritis and hypertrophy. In this case the bilateral enlarged shadow could be explained by the pyonephrosis on the left side, and by hypertrophy on the right side.

There may be great difficulty in distinguishing between polycystic kidney and neoplasm, since not infrequently but one polycystic kidney is found, on palpation, to be definitely enlarged. The other kidney, even though polycystic, may either be only slightly larger than normal, or so situated that it cannot be definitely palpated. It should also be remembered that with

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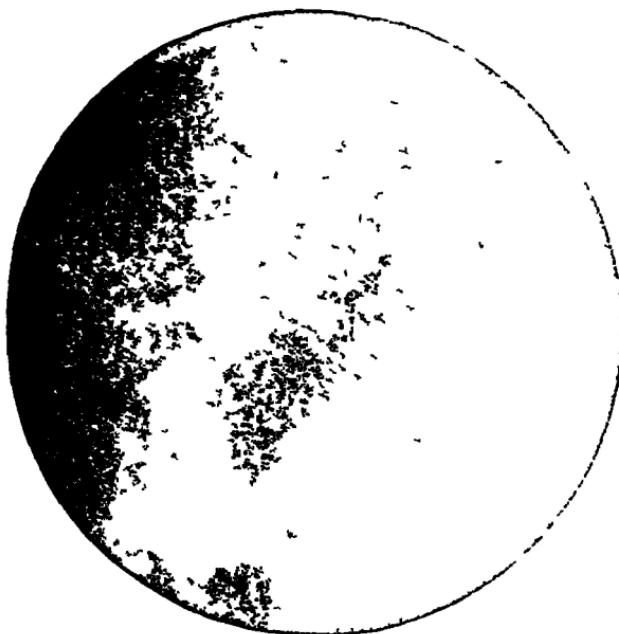


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a definite renal tumor palpated on one side, an apparent renal tumor may be found on palpation of the opposite side, which may be due to any one of numerous extrarenal conditions. In such cases pyelography will be of great diagnostic value (Fig. 174).

The pelvic deformity occurring with polycystic kidney is caused by compression of the outline of the pelvis and calices, by the cysts. As a result, various bizarre types of deformity may appear in the pyelogram, which, although they are usually recognizable, may be confused with the deformity caused by renal neoplasm. An abbreviation of one or more calices is very common. Elongation of the calices is also frequently present, and is usually accompanied by broadening, rather than the narrowing observed with neoplasm. The tapering termination of the calices found with neoplasm seldom occurs with polycystic kidney. In case of doubt, a pyelogram should be made of the other kidney later, never simultaneously. If the pelvis of the opposite kidney is normal, polycystic disease is excluded, for a normal pelvis is never observed with a polycystic kidney.

**Case 2** Renal tumor.—A man, aged forty-six years, began to lose appetite and weight eight months before he came to the Clinic. He also had general malaise. Two months before he noticed a mass in the left side of the abdomen. No urinary symptoms were present. On examination a fairly fixed mass was palpated in the left upper abdomen, about 12.5 cm in diameter, which was suggestive of either renal neoplasm or an extraperitoneal tumor. The tumor was peculiar in that it seemed, on palpation, to be made up of two parts. Cystoscopic examination was negative. A pyelogram of the left kidney revealed upward displacement of the renal pelvis with a deformity which was not typical of renal neoplasm. The marked upward displacement and doubtful nature of the pelvic deformity led us to consider the possibility of an extrarenal tumor, which can displace the pelvis in any direction in much the same manner as renal tumor (Fig. 175). At operation it was found that the double mass was due to hypernephroma of the kidney, and an adjacent metastatic growth almost as large. It was manifestly inoperable.

**Comment**—If the pyelogram shows a bizarre position, both of these possibilities should be considered. As a rule, however, the type of abnormality in the pelvic outline permits identification of the tumor (Fig. 176). In cases of doubt, another



Fig 175—Extrarenal tumor with marked renal displacement

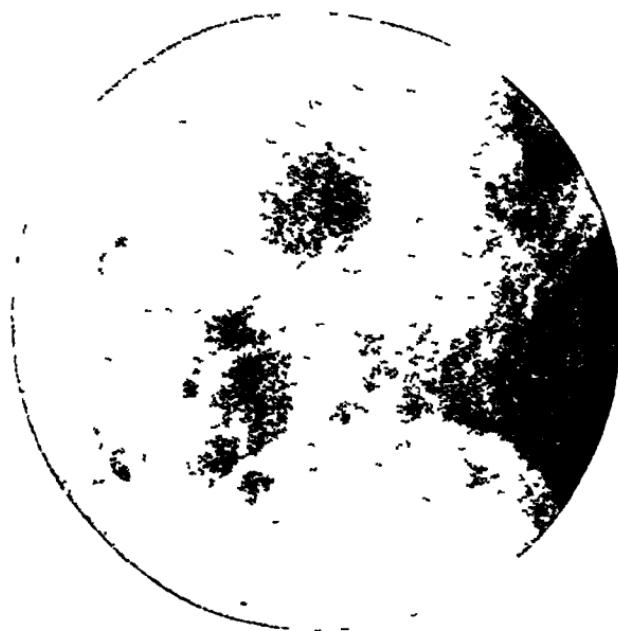


Fig 176—Hypernephroma

valuable method of diagnosis is the differential renal functional test. With a renal tumor of this size, there will be marked reduction in dye return from that kidney, with more or less increase from the opposite normal kidney. If the tumor is small, or is confined to one pole of the kidney at some distance from the renal pelvis, the difference in function may not be sufficient



Fig. 177.—Metastasis to the lungs from hypernephroma

to be of practical value. In order to be significant clinically, the difference in dye return should be at least 50 per cent. Lesser degrees of difference in function can often be explained by technical error or by reflex irritation. Even with marked difference in function, care must be taken in the interpretation to see that all technical errors are excluded. Phenol-sulphone-phthalein probably offers the most practical method of differentia-

tion, and is more accurate than indigocarmine. Since in this case the phenolsulphonephthalein return was 20 per cent from the right kidney and only 3 per cent from the left, a clinical diagnosis of left renal neoplasm was made. We were unable to explain the apparently double nature of the tumor which, on palpation, appeared to be caused by two retroperitoneal masses.

Metastasis into the adjacent tissues of this type is quite common with hypernephroma, or clear-celled alveolar carcinoma. As a rule it is diffuse and of limited extent and only rarely causes a tumor as large as that in Case 2. Its presence can often be inferred by its degree of immobility. A fixed, rigid tumor usually offers a poor prognosis. Metastasis to the lungs is also common with renal neoplasm (Fig. 177). This should be excluded by routinely x-rayng the chest whenever neoplasm is suspected, since the metastasis may produce no other clinical symptoms. Discovery of such metastasis has saved a needless operation in many of our cases.

**Case 3 Ureteral tumor**—A man, aged fifty-four years, had had hematuria much of the time for a year before coming to the Clinic, and also moderate dysuria. Cystoscopic examination was made elsewhere three months before, and a papillomatous tumor was found protruding from the right ureteral orifice. The urine from the kidney was hemorrhagic, the left kidney being apparently normal. A diagnosis of ureteral tumor was made, fulguration was attempted. The hematuria disappeared for a week or two, and then recurred and remained constant. The patient came under our observation three months later.

Physical examination, including roentgenographic studies, was negative except for slightly hemorrhagic urine. The cystoscopic data were as follows: a moderate degree of cystitis in several areas; the right ureteral orifice was inflamed and somewhat edematous, there was no evidence of a papilloma. The urine from the right orifice was slightly hemorrhagic, that from the left was normal. There was no obstruction to the ureteral catheter as far as the renal pelvis. A pyelogram of the right kidney showed a moderate degree of pyelectasis; the ureter was well dilated in its lower portion, and only slightly dilated in the upper third (Fig. 178). The type of pyelectasis was similar to that observed with obstruction in the lower ureter, and was characterized by a relatively greater dilatation of the calices than the pelvis (Fig. 179). The phenolsulphonephthalein return in fifteen minutes from the right kidney was 8 per cent, and from the left, 15 per cent. An exploratory operation for either papillary epithelioma of the renal pelvis or ureteral neoplasm was advised.

and clinical data of the underlying condition. In cases of doubt, biopsy of a specimen removed would clear the diagnosis. It is evident that the papilloma removed was of an inflammatory nature and secondary to chronic ureteritis. Had the specimen been taken from the polyp for biopsy, its inflammatory nature would, of course, have been revealed. Granulomas and polyps



Fig. 180.—Papillary epithelioma of renal pelvis.

resulting from ureteral stone will sometimes resemble neoplasm thus masking the underlying cause. This is particularly true if the x-ray fails to show a shadow, or if the situation of the growth in the median line leads to its being considered extra-ureteral. Granulomas observed with tuberculosis may also be confusing, and have frequently been taken for papilloma.

Any treatment, such as dilatation or lavage, would not

have given permanent relief from renal infection so advanced and widespread as that present in this case

**Case 4** Renal Lithiasis—A man, aged forty-two years, had complained for six years of a frequent dull pain referred to the right side of the spine, at about the level of the crest of the ilium, and usually coming on after strenuous exercise. On several occasions the pain was accompanied by hematuria. It was never referred to the left loin.

The general examination was negative. A roentgenogram of the urinary tract disclosed three shadows of stone in the left renal area, one was unusually large and round, two were small. On cystoscopic examination, the right kidney was found to be quite normal. Urine catheterized from the left kidney contained only a few pus cells. In the differential renal functional test, using indigocarmine, the dye return from the right kidney was normal, and there was but a trace of color from the left during fifteen minutes. The natural inference would be that because of the size and number of stones, and the evidence of marked disturbance of renal function, a left nephrectomy would probably be indicated.

At operation the left kidney was found to be greatly hypertrophied, being about twice normal size. It was markedly elongated, and the lower pole was situated across the vertebrae so that at first it was thought to be a horse-shoe kidney. The increase in size of the kidney was suggestive of a compensatory hypertrophy, but this could not be possible, because on clinical examination, the other kidney was found to be normal. A large stone (73 gm.) was removed through the pelvis without much difficulty, and subsequently two smaller stones were removed.

*Comment*—This case graphically teaches us the possibility of error in interpretation of the differential renal functional test. All of our present dye tests have a tendency to exaggerate the degree of damage done in the kidney. While the indigocarmine is a coarser test than phenolsulphonephthalein, nevertheless the latter is not much more reliable in similar circumstances. Owing to the reflex irritation caused by renal stones or acute renal inflammatory processes, it is well known that there is a marked temporary reduction in the dye secretion. It has been my experience that when there is complete absence of dye, there is usually widespread damage, and when there is a normal dye return, the kidney is usually normal. Intermediate values are very inaccurate.

In this case the kidney was almost twice as large as normal, and the renal tissue was quite normal, at least on microscopic examination, and yet there was no dye return, apparently owing

to reflex irritation caused by the stones. This illustrates clearly how careful one must be in interpreting renal functional tests. It can usually be inferred that the kidney is largely destroyed when the urine is so purulent that it looks like tooth-paste. A clear urine or a turbid urine, however, is not necessarily significant. The discovery of a large kidney, such as was present in this case, is suggestive of compensatory hypertrophy, because

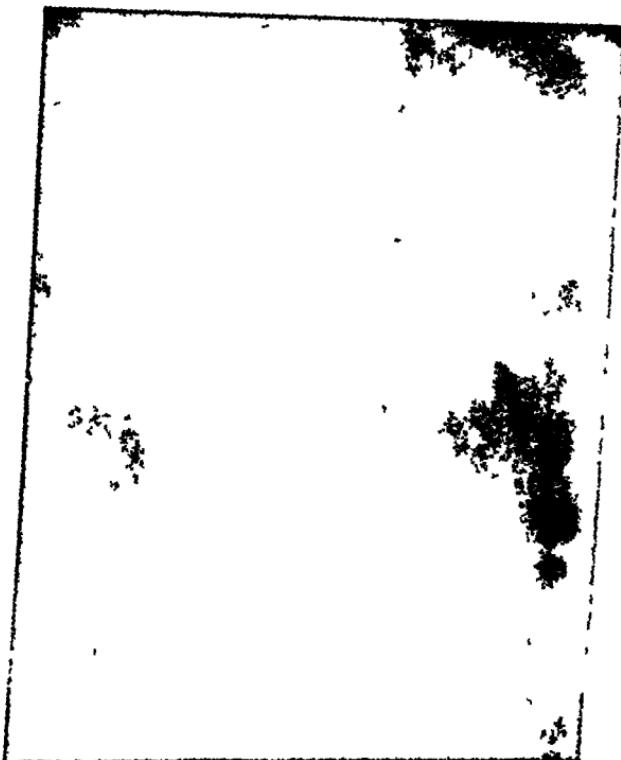


Fig. 181.—Large, round renal stone.

of the diseased right kidney. The cautious surgeon would hesitate long before removing the kidney. In this case, however, the dye test of the opposite kidney appeared to be normal. Of considerable interest was the radiation of the pain, which was referred largely to the opposite side. Such symptom suggests the possibility of a horseshoe kidney. The localization of the pain might be explained by the fact that the kidney

was situated partially over the spine, but the pain was probably of extrarenal origin

Finally, this case illustrates that the degree of destruction of the renal tissue does not depend so much on the size of the stone as on its shape and the extent of interference with drainage. Round stones will usually cause much less damage than the branched, irregular types, since they seldom interfere so much with the drainage. Round stones, even those of huge size, can usually be removed without much damage to the renal tissue (Fig. 181). A branched stone of similar size could hardly have been removed without much damage.

**Case 5** Renal tuberculosis.—A man, aged thirty-two years, came to the Clinic because of urinary frequency, without dysuria, which had persisted for nine months. His home physician reported that there had never been blood or pus in the urine. In every case of persistent urinary frequency, urinary tuberculosis must first be excluded. If, in a young adult, there has been persistent frequency day and night, together with dysuria and pyuria, it should be assumed that the condition is tuberculous, until it has been proved otherwise. Examination of the genitalia for evidence of tuberculosis is the first essential, and in this case the epididymes were both soft, and the prostate gland was practically normal. In the region of the right seminal vesicle, however, there was definite evidence of induration, and a deformity of the vesicle, which was suggestive of tuberculosis. Some evidence of involvement of the genitalia is found in about 90 per cent of male patients with renal tuberculosis. It should be noted in differential diagnosis that involvement of the genitalia with tuberculosis is almost always asymmetrical. That is, one lobe of the prostate is larger and more involved than the other, one vesicle is usually more diseased, and one epididymis is larger and more diseased than the other.

In the first examination of the urine only a few pus cells were found, and the search for *Bacilli tuberculosis* was negative. Roentgenograms of the urinary tract were negative for possible calcareous areas of tuberculosis. Cystoscopic examination revealed only a very slight areal cystitis, and both ureteral orifices were normal. On ureteral catheterization there were only two pus cells in the specimen from the right kidney, and none in the left. The phenolsulphonephthalein return during fifteen minutes was 15 per cent from both kidneys. In cases of renal tuberculosis, one expects to find reduction of function in the kidney involved, and pus in the catheterized urine, as well as a variable degree of cystitis. In the urine catheterized from the right kidney *Bacilli tuberculosis* were found, which made the diagnosis of right renal tuberculosis evident. To corroborate the diagnosis, however, a right pyelogram was made, which showed a deformity suggestive of tuberculosis. At operation the right kidney was removed and, on section, several small discrete areas of definite tuberculosis were found in the renal parenchyma.

*Comment*—Patients often come to us who have considered themselves healthy until they applied for life insurance and were told that pus was found in the urine. In ascertaining the origin of the pus, the urine may have been stained for *Bacilli tuberculosis*, and when found, the patient frequently comes to us for verification. Quite often neither pus cells nor *Bacilli tuberculosis* are found in the urine at the time of the first examination, and it is difficult to decide whether the previous examina-



Fig. 182.—Tuberculous right kidney

tion was in error, or whether there had been a passing shower of bacilli and the condition was now in a stage of quiescence. A careful search of repeated specimens of urine for *Bacilli tuberculosis* is essential, and if negative, repeated guinea-pig inoculations of urine may be necessary before tuberculosis can be excluded. The pyelogram may be the best method immediately available for establishing the diagnosis, since, if renal tuberculosis is present, there will usually be some pelvic deformity. This deformity may consist of either dilated calices,

evidence of cortical necrosis, or ureterectasis at the uretero-pelvic juncture (Fig 182) Guinea-pig inoculation is, of course, more accurate as a rule, and should be made when the other clinical data leave the diagnosis in doubt The necessary delay involved is the greatest objection to inoculation

Recently a patient came under our observation who had no urinary symptoms whatever, and whose local physician had accidentally found *Bacilli tuberculosis* in the urine, which was otherwise negative At examination here, no physical evidence of tuberculosis was found, and urinalysis revealed no pus cells In the catheterized urine from the right kidney, however, acid-fast bacilli were found on two occasions A right pyelogram failed to show any evidence of deformity in either the pelvis or ureter In order to ascertain the identity of the bacilli found, guinea-pig inoculations were made, and were found to be negative Needless to say, it would not be justifiable to operate because of the finding of acid-fast bacilli in the urine, without other corroboratory evidence of renal tuberculosis

Such cases illustrate the necessity of employing all the clinical data at our command in establishing a diagnosis when renal tuberculosis is suspected A localized tuberculous process in a kidney of this type may be most difficult to diagnose and unquestionably many similar cases are being overlooked The question frequently arises whether operation is warranted when *Bacilli tuberculosis* are found in the urine, and when there is no other evidence of renal tuberculosis As a rule, of course, there is other corroborative data, but if not, one is justified in delaying operation until there is further evidence It is remarkable how much renal destruction may be found at operation, when there has been but little clinical evidence of tuberculosis

The pendulum of opinion has swung back and forth with regard to the bilateral occurrence of renal tuberculosis At first it was believed that renal tuberculosis was always bilateral Later it was believed that bilateral tuberculosis was rarely present, and that the condition was, primarily, almost always unilateral Of late we are recognizing that primary bilateral

tuberculosis occurs much more frequently than we had supposed. The results of guinea-pig inoculations which have been made of the supposedly normal kidney lead us to believe that the infection, in a considerable number of cases (approximately 20 per cent), is primarily bilateral. This, however, does not interfere with operation when one kidney is found, on cystoscopic examination, to be definitely diseased, and the other apparently otherwise normal.

## THE DIFFERENTIAL DIAGNOSIS IN CASES OF ECTOPIC ADENOMYOMA IN THE GROIN

WILLIS S LEMON AND ARTHUR E MAHLE

**Case 1**—A woman, aged thirty-eight years, has been examined at the Clinic on five occasions. She first came to the Clinic because of sterility. She had been married eight years, but had never become pregnant. The menses were normal in onset and were occurring at intervals of twenty-eight days, whereas within the ten years previous to examination, they had occurred every twenty-four days. The menses lasted for five days and were usually profuse during the first twenty-four to thirty-six hours, and there was dysmenorrhea for a few hours to a day preceding each period. Fibrous tumors of the fundus of the uterus were found, these were known to have been present for at least four years.

At the time of the second examination, the dysmenorrhea had decreased, but metrorrhagia had appeared, although only occasionally. The tumors had not increased in size.

At the third examination, when the patient was forty-two years of age, the periods were becoming irregular, appearing at intervals of from twenty-one to twenty-seven days, with a decrease of dysmenorrhea and an increase in the amount of flow. It was found that a second type of tumor had developed which could be seen and palpated in the right inguinal region. This tumor was about 2.5 cm in diameter, very hard, and tender during menstruation. A very small tumor, about 0.5 cm in diameter, was found in the left groin.

On the fourth examination, a year later, the tumor in the right inguinal region had increased in size, and had become irregular and slightly movable. Between menstrual periods it was not tender to palpation, although it became tender with a sensation of soreness during the periods. The character of the growth was not determined, the possibility of enlarged lymph nodes was considered.

Operation was performed June 30, 1919, at which time multilocular masses were found to be so adherent to one another and to the femoral artery that it was necessary to dissect the mass away and remove it in one piece. The pathologic examination disclosed adenomyoma of uterine type.

The patient returned later, because of recurring adenopathy in the right groin with soreness and some enlargement during menstruation, but only a very small mass was found external to the operative scar, and there was not sufficient evidence to warrant surgical removal, either of it or of the uterine fibromyoma.

**Case 2**—A woman physician, aged fifty years, who was unmarried, and whose menstrual life had been normal, found the flow was becoming increasingly profuse. Four years before examination at the Clinic, a uterine polyp had caused continuous bleeding until it was spontaneously evacuated. There had been no dysmenorrhea. Fibroid tumors of the uterus, however, had been diagnosed as long as three years before her examination at the Clinic, and an appendiceal abscess had been drained twenty-five years before. A fibrous tumor had been palpable through the abdominal wall during the last year, and seemed to be growing rapidly. Some years after the appendectomy drainage, the scar had begun to show evidence of contraction, and was painful during menstrual periods. Four years before, two tumors had been noticed in the region of the scar, they had the characteristic appearance of lymph nodes, with sluggish growth.

At the time of our examination, the scar was contracted, and the skin in the neighborhood was adherent. There was also induration, and the general appearance was that of a keloid.

Operation was performed for multiple fibromyoma of the uterus, left oophoritis, salpingitis, chronic appendicitis and a right indirect inguinal hernia. A subtotal hysterectomy, left oophorectomy, salpingectomy, appendectomy and herniotomy were done. Later, the necrotic and inflammatory mass, resembling a keloid, was removed from the right groin, and thought to be an incarcerated femoral hernia or infected lymphatic nodes. However, the inflammatory mass proved to be indurated, it was about 5 cm long and 1.5 cm wide. Underneath the skin, however, a dark necrotic cystic tissue was found which extended to the femoral opening. The pathologic examination disclosed adenomyoma of uterine type.

**Case 3**—A woman, aged forty-two years, came to the Clinic in September, 1921. She had been married for eight years, and had had two miscarriages, one at six weeks, and the other at four months. The menses had always been normal. She complained of migrainous headaches, and of a left inguinal hernia.

It was found that she had bulging of the left inguinal ring produced by two hard masses, about 2.5 cm in diameter, that could be palpated at the external opening of the inguinal canal. Similar tumors were found in the femoral fossa, and gave the impression of nodes involved by metastatic growth. Examination of the pelvis did not reveal evidence of abnormality.

At operation, the tumor of the left groin was removed, and the femoral hernia was repaired. The pathologic examination showed adenomyoma of uterine type.

#### DISCUSSION

It will be observed that, in each of the cases described, the tumors have been confused with adenopathies of the groin. Adenopathies in this region naturally fall into three groups—the inguinal, the femoral, and the iliac. The inguinal glands are most readily infected by disease in the area from which

the nodes receive their drainage, for this reason tumors of the lymphatic nodes in the inguinal region (in the subcutaneous tissue around Poupart's ligament) require examination of the external genitals, anus, umbilicus, lower abdomen, back, and upper third of the thigh. The femorals are less commonly involved, and their enlargement usually indicates primary disease in the leg, below the upper third of the thigh. These nodes are found in the neighborhood of the saphenous opening. Enlarged lymph nodes of the groin are nearly always multiple, usually subcutaneous, and of such character that they are almost always recognizable. Adenopathy in the iliac region is sometimes confusing, and is commonly secondary to involvement of the inguinal or femoral glands, but may be primarily infected from disease within the pelvis. They lie above and deeper than the femoral or inguinal tumors.

In two of the cases reported here, femoral hernia was considered as a diagnosis previous to operation, in one instance, there was an error in diagnosis. Such an error is very easy to explain, provided a single mass is present at the saphenous opening and adherent to it. It may be impossible to distinguish an irreducible femoral hernia or a hydrocele of a hernia sac from the other types of tumor. It is advisable in all such questionable conditions to observe the note on percussion, because hernia is usually resonant or tympanitic, and other tumors, dull. This, however, is not a diagnostic point, providing the hernia contains only omentum. Under that circumstance, surgical exploration alone can determine the character of the tumor. This is also true of lipoma that sometimes occupy this position, they are soft and displaceable. However, the possibility of an impulse on cough may make their recognition extremely difficult, omental hernia may be diagnosed and the error found only on exploration.

#### THE USUAL CAUSES OF INGUINAL ADENOPATHY

Cabot, in his discussion of tumors of the groin, says, "The normal wear and tear of existence in civilized communities produces enough infection or subinfection to bring about some

enlargement of the gland without our being able to say that any disease has affected the individual or his glands" This is true of one type of adenopathy, namely, that produced by mechanical or chemical irritation, to the traumatism of long continued pressure from a truss, or in those of unclean habits who may harbor parasites of various types Septic infection in the region drained by the node produces another type of tumor which, however, has certain characteristics that make it easy of identification The original focus is discovered without difficulty and its removal usually results in immediate subsidence of the inflammation in the node If, however, the inflammation does not subside, the node quickly suppurates and within a few weeks an abscess is formed Another type of tumor of the nodes is produced by tuberculous infection and is not common in this region

At least three types of tuberculous adenopathy have been described, any of which might affect the inguinal nodes, although as a rule they involve the nodes of other areas Among these is the type described by Hilton Fagge, in which the nodes are enlarged, ovoid, discrete and without tenderness, but on excision are found to have lost all of their original architecture, and to be composed of a central necrotic mass and a surrounding layer of firm fibrous tissue A second acute type is described by Longcope, in this, the nodes which are discrete, movable and occupy the usual location of lymphatic nodes, simulate those of Hodgkin's disease On biopsy they are found to be composed of very large numbers of small miliary tubercles The third and common type comprises those nodes which suppurate late, often three to four months or many years following their incipiency After suppuration, they present the usual evidence of induration with the characteristic ragged sinus formation

A fourth type of adenopathy is produced by syphilis Such nodes are hard, usually associated with a chancre, but not found in the groin in testicular involvement unless the usual phenomena of fungous formation and involvement of the scrotum occurs The Wassermann reaction or the presence of spirochetes

makes their diagnosis certain. One discrepancy should be observed, however, namely, that a suppurating bubo, supposedly from gonorrhreal infection, may be syphilitic in character and later take on indurative characteristics.

A fifth type comprises those nodes developed during specific disease, such as rubella and plague, and are of a character that need not be described in this discussion.

The sixth and seventh types, reported by French, comprise those nodes affected by Hodgkin's disease, lymphatic leukemia, or lymphosarcoma. The usual clinical examinations of the patient is sufficient to distinguish them from other types. However, in one case I experienced some difficulty because the lymphatic enlargement was the earliest sign of lymphosarcomatous involvement and an accurate diagnosis could not be made by clinical methods. Biopsy was required to determine the exact nature of the tumor. Later in the progress of the disease in this patient, all other gland-bearing areas became involved and metastatic nodules likewise appeared on the skin, so that a diagnosis could be made without difficulty.

Adenopathies may be produced by metastatic involvement of the lymphatic nodes and are of two characters carcinomatous and sarcomatous. This type is important because the node may be much more easily observed than the primary that produced it, particularly in the inguinal region, for a small malignant growth about the anus, or a small melano-epithelioma between the toes may be unobserved by the patient, yet produce a metastatic nodule in the inguinal lymphatic nodes. These nodes are hard, progress very slowly, and usually are adherent to the structures immediately surrounding them. They may fungate, but only late in the progress of the disease.

The melanotic type are probably most important and are distinguished as a rule by their bluish color. We have observed three instances at the Clinic, in which the primary disease appeared about the toes, and each was without pigment, in two instances the metastatic nodes themselves were free from the usual melanotic characteristics. In each instance, these tumors were firm to the touch, and densely adherent to the deeper structures.

One other type of tumor in women must be considered, namely, the fibromyoma of the round ligament which may appear in the region of the canal of Nuck, and be confused with a thick-walled hydrocele. In one instance, a tumor in this region proved to be the ovary itself, which had descended into the canal of Nuck, on replacement, bloody fluid was discovered in the sac.

Of the various other types of tumor, those found in males will be omitted, because peculiar growth in the cases presented here, has not, in our experience, appeared among males.

Aneurysms or other vascular swellings demand consideration in differential diagnosis. These, however, are usually distinguished by the ordinary methods of physical examination, by the fact that they can definitely be proved to be part of the vascular mechanism, lying in the areas occupied normally by the great vessels, and by a history of specific disease, verified by serologic tests. The pulsation in itself may be confusing because other tumors located about the femoral artery may have conveyed to them a pulsation simulating the expansile type.

#### DIAGNOSTIC CHARACTERISTICS

Although in differential diagnosis between ectopic adenomyoma of the groin and adenopathies of the groin, the classification described is of particular value and each pathologic condition must be considered, yet there are certain factors relating to ectopic adenomyoma in the groin that make them characteristic. The most important of these is the fact that such growths have appeared only in women, that they are associated with menstrual disorders, and in two instances with actual tumor formation within the pelvis. They are sluggish, slow growing tumors of benign character, taking years to develop, and without disagreeable symptoms, excepting during the menstrual period, when they take upon themselves the same functions that are characteristic of the uterine mucosa. The tumor enlarges and its swelling produces discomfort or real pain, the growth becomes tender to the touch and cysts form as small bluish areas beneath the epithelium. These are not only visible,

but palpable, and on incision contain blood. A negative characteristic is worthy of consideration. In contradistinction to tumors of the nodes, they are found to appear in areas not occupied by lymph nodes. These characteristics suggest to the examiner that the tumor itself must in some way be related to the uterus, whose mucosa alone has the inherent possibility of periodical engorgement. Such a tumor then must be composed of tissue derived from, and identical with, the uterine mucosa, and therefore may be classified with the adenomyomas, although in an unusual location for such tumors. This is not so surprising, however, inasmuch as ectopic types of adenomyomas have been described.

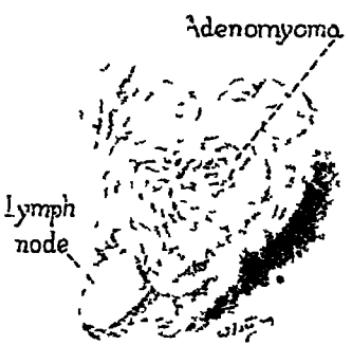


Fig. 183 (Case 3) — Adenomyoma adherent to lymph node (See Fig. 184)

In each of the cases described the tumors were histologically typical adenomyomas of the uterine type.

In Case 1, the tissues consisted of an adenomatous mass, 4 cm in diameter, which was adherent to the inguinal lymph nodes (Figs. 183, 184). The cut surface was gray and fibrous, and crossed by streaks of grayish white tissue between which were cystic spaces filled with dark brown to black serum, resembling old blood (Fig. 185). Microscopically the stroma consists of fibrous connective tissue, a few muscle bundles, and here and there glandular alveoli, circular, oval or irregular in shape. The epithelium is cuboidal to columnar in shape, some of the

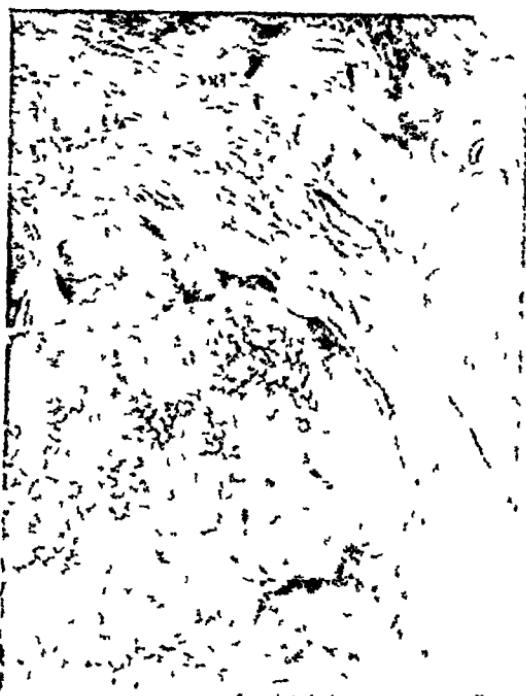


Fig. 184 (Case 2).—Low power photomicrograph showing relationship of adenomatous tissue to lymph nodes. Note degenerative changes in substance of lymphoid tissue.



Fig. 185 (Case 1).—Typical gross appearance of an ulcer in tumor.

cells being ciliated. The gland spaces in some areas are surrounded by a cellular stroma, while in others the epithelium rests on fibrous tissue without the intervening cellular stroma (Fig 186). On sectioning different areas of the tumor, it was found that the cells about some of the gland spaces were larger than those seen in normal endometrium, that the cytoplasm stained more clearly, and the nucleus was larger, with very little chromatin staining substance or few chromatin masses. These cells resembled the so-called decidual cells seen in the endometrium of the uterus and were quite easily distinguished.

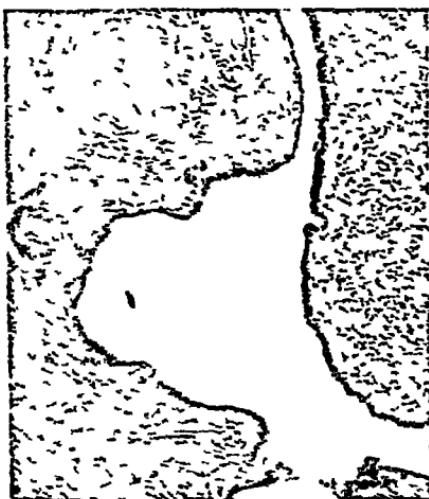


Fig 186 (Case 1)—Adenomyoma with decidual cell formation in cytogenous mantle around glandular space

from the more usual type of cell seen in other areas (Fig 187). The patient was not pregnant at the time of the removal of the tumor from the groin. We have seen this reaction in the endometrium of other patients, not pregnant, and therefore feel that it is not necessarily related to pregnancy. These findings are of no diagnostic importance, but tend to show further the close relationship of ectopic adenomyoma to uterine tissue, and are of interest in considering the manner of their development.

Other cases in which there were decidual cell changes have been reported by Meyer and others. Lockyer reported a case

of decidual reaction in the medulla and cortex of the ovary in a case of ovarian pregnancy, and mentions a case reported by Griffith at a meeting of the Obstetrical and Gynecological Sections of the Royal Society of Medicine of an adenomyoma of the recto-vaginal septum of a woman who was pregnant. Sections showed large masses of typical decidual cells between muscle layers and surrounding some of the gland spaces.

Cullen reports a case of tubal pregnancy in the left tube and a diffuse adenomyoma in the right uterine horn, the stroma cells around the adenomatous areas having undergone typical



Fig. 187 (Case 1) — High power photomicrograph of decidual cell formation

formation. The gross and histologic picture of the tissue in Cases 2 and 3 was similar to that in Case 1, except that no decidual-like tissue was found. The lymph node which was adherent to the adenomatous tissue showed rather marked degenerative changes and replacement of the lymphoid tissue by fibrous connective tissue. The glandular tissue is seen in close proximity to the lymph node (Fig. 184).

#### SUMMARY

It will be observed that the tumors in the groin are very similar to the nine cases of adenomyoma of the abdominal wall

that were described in a recent report. Their structure and behavior are similar to those of normal uterine mucosa. They are congested during the menstrual period and produce cysts which contain dark blood undergoing the same cyclic changes as uterine mucosa, and in all histological respects simulate that tissue. They may be mistaken for adenopathies. No explanation can be given for the development of the growths in the peculiar location described.

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## TUBAL INFLATION IN A CASE OF STERILITY

LAWRENCE M RANDALL

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A woman, aged twenty-nine years, registered at the Clinic primarily because of sterility. She had been married seven years. Her menses began at the age of fourteen and had always been regular. When she had been married nine months, an abortion was induced to terminate a two months' gestation. This procedure was entirely successful from her viewpoint, as she had no fever or chills, and was in bed only a few days. There was, however, a somewhat foul odor to the uterine discharge for about a week. Since this time her general health had been excellent, but, with no precautions against pregnancy, she had failed to conceive. During the last five years, she had visited three physicians, seeking relief from sterility. The first physician performed dilatation and curettage, the second recommended artificial insemination, and the third an exploratory laparotomy.

The patient was 5 feet 4 inches tall, and weighed 120 pounds. The general examination including the laboratory tests, and serum Wassermann test, was negative. Pelvic examination revealed the normal external genitalia of the adult female. Bartholin's glands were not palpable and no pus could be milked from the urethra. The perineum was snug and elastic, the vaginal mucosa normal to touch, and the fornices moderately deep. The cervix was in good position, slightly lacerated on the right. The uterus was normal in size, shape, and consistency, anteverted, and inclined slightly to the right. The ovaries were palpable but not enlarged, no thickening or enlargement of the tubes could be made out, and there was no evidence of an old parametritis. A medium-sized applicator-

passed easily into the cervical canal. The secretion in the cervix was clear, but not tenacious or inspissated. A postcoital specimen contained normal spermatozoa at the end of half an hour. The vaginal secretion was mildly acid. Examination of condom specimen of semen disclosed spermatozoa normal in number, motility and morphology. It should be borne in mind, in this connection that fully 50 per cent of sterile marriages may be attributed to the male, hence a critical examination of the husband should always be made.

It was decided to perform a tubal inflation in this case. This should be done about midway between the menstrual periods. With proper selection of patients, no ill result need be feared. The contraindications to tubal inflation are few and definite. These are acute or subacute infection of the pelvic organs, an old pelvic infection in which a great amount of discomfort or an elevation of temperature is noted following a thorough bimanual examination, the presence of marked endocervicitis, the demonstration of a lesion in the pelvis which would be a serious complication to pregnancy, and serious disease of the heart or lungs, which might lead to complications at the time of inflation, and also would render pregnancy undesirable. Obviously any uterine bleeding is a definite contraindication.

In inflating we employ the technic of Rubin in preference to modifications of his method, or other methods, since with it there seems to be less chance of error and the interpretation of findings is easier. Carbon dioxide is conducted from the tank to the water trap from which one connection goes to the mercury manometer and the other to the canula. The rubber tube leading to the canula is provided with a needle valve to permit the release of pressure. The water trap permits measuring the amount of gas used and the rate of flow. The necessary instruments for the test are a bivalve speculum, tenaculums, dressing forceps, uterine canulæ (two sizes), sponges, and applicators. To the Keis-Ultzmann canula has been added a metal collar against which the rubber urethral tip rests, thus in many instances the tenaculum is not needed. Enough pressure can

be maintained against the cervix to prevent the escape of gas without danger that the canula will slip suddenly into the uterus. The tenaculum is sometimes necessary, but it adds a factor of discomfort and should be avoided, if possible.

The gas passes through the trap at the rate of two bubbles or pulsations a minute, each bubble representing 40 c.c. of carbon dioxide. This is the rate used for the first two elevations of pressure, later it is increased to four. The bivalve is inserted, the mucus cleaned from the cervix the external os and cervical canal painted with half strength tincture of iodin and wiped dry. The canula is inserted until the rubber guard fits snugly against the external os and connection is made with the tube to the gas supply. The mercury column rises slowly. Slow elevation of pressure is important. Should gas be admitted rapidly, the amount of carbon dioxide forced into the uterus is much greater than can be carried away by even normal tubes, and the reading on the manometer will be not that of the pressure necessary to open the tubes, but of back pressure in the uterus. Moreover, rapid admission of gas with consequent sudden distention of the uterus produces a definite colic which is much more pronounced than that experienced with a slow gradual rise in pressure. When the gas pressure reaches 100 mm. of mercury, the patient experiences a cramping sensation just above the pubes in the median line. This gains in severity as the pressure increases, until at 200 mm. it causes discomfort. The advisability of using a pressure of more than 200 mm. is doubtful. Tubes have been subjected to 300 mm. of pressure without ill result, but it has been proved that tubal rupture is likely to occur with pressure above 200 mm. The needle valve is opened, and the pressure slowly returns to zero. The time consumed in raising the pressure to 200 mm. was ninety seconds. The pressure is again raised slowly and the patient complains of colicky pain extending to the left side as well as to the median line. This procedure is repeated five times with the same result. On removing the canula from the cervix, gas bubbles out. No bleeding is evident. The cervix is again painted with tincture of iodin, half strength, and wiped dry. The patient sits

up on the edge of the table and has only a slight cramp in the lower abdomen and no shoulder pain

A second inflation was performed and the same picture was noted, thus justifying a diagnosis of bilateral occlusion of the fallopian tubes. One unsuccessful inflation does not seem sufficient to warrant a positive statement that the tubes are closed, and we always ask to repeat the test. No serious attempt is made to localize the site of closure of the tubes from the subjective sensations of the patient. The idea has been advanced that the pelvic cramp could be utilized for this purpose, the assumption being that the pain would be more noticeable on the closed side. It is obvious that this would depend entirely on the site of closure. Were it an occlusion at the fimbriated end, there would be distention of the tube, and colic. However, were it near the uterus, actually at the uterine end, or in entire obliteration of the tubal lumen, distention of the tube and consequent colic would be absent. The same would obtain with one patent and one non-patent tube, in which instance the gas would escape through the sound tube. In this case, however, to predict the condition of the tubes from the basis of a median line cramp with some extension to the left, might lead to the conclusion that the left tube is occluded rather far out, probably at the fimbriated end. The right side was entirely free from cramp, but as no gas was forced through, it might be concluded that the obstruction in the right tube was close to, or actually at the uterine end. Auscultation over the tubal areas is also employed by certain observers to detect the escape of gas into the abdomen. It has been held that the degree of closure or stenosis can be estimated by the pitch of the note of the escaping gas.

At the Clinic the manometer reading with the gas flowing, the reaction of the patient while inflation is in progress, and the appearance of shoulder pain following the procedure are relied on for interpretation. If doubt exists as to the result, an x-ray examination of the upper abdomen is made shortly after the patient is placed upright. In case of patency, the pressure during inflation rises to a variable height even to 200 mm. of mer-

cury, then falls rather sharply to a lower level, remaining fairly constant until the desired amount of carbon dioxid has been forced into the abdomen (80 to 160 c c) The average patent tube will permit the passage of gas at pressures of from 40 to 80 mm Often, however, the tubes seem to be partially occluded, the gas passing through at higher levels of pressure Women with non-patent tubes nearly always have more discomfort during the inflation than do those without occlusion With patent tubes, the shoulder pain following inflation is characteristic. The patient, on sitting up following the introduction of from 80 to 160 c c of carbon dioxid will, in a few seconds as a rule, complain of definite pain in either one or both shoulders which may radiate to the neck and down the arms Doubtful interpretations are corroborated by x-ray or fluoroscopic examination If gas has entered the peritoneal cavity, a shadow is evident with the patient in the upright position Usually it is seen on the right side, and appears as a definite bubble separating the liver from the diaphragm

As to the management and treatment in this case, three courses are open (1) the employment of hot douches and hydrotherapy to the pelvis, since by leaving the condition more or less to natural healing processes pregnancy sometimes occurs, (2) a plastic operation on the fallopian tubes, and (3) repeated tubal inflations with the hope of opening the tubes With regard to the first course the possibilities for cure are remote The results from a salpingostomy are also doubtful It seems, therefore, that the best advice to this patient is at least four more inflations with the idea of possibly opening the tubes, failing this, operation may be considered

The employment of tubal inflation with the abdomen open is also of value in cases in which a preoperative diagnosis of closed tubes has been made by inflation It localizes the offending adhesions, definitely shows the point of occlusion, and opens up the tube after the adhesions are freed with far less trauma than is incident to the passage of a probe It is also possible, with the abdomen open, to elevate the pressure to a higher level than one would feel free to do under ordinary circumstances,

thereby possibly opening the tube with the minimum of trauma

In many cases of sterility, the etiology is obscure, in a few we can arrive at as definite a conclusion as we have in this patient. Added to the natural difficulty which each case presents is the idea still prevalent among the laity, and not defunct in the medical profession, that sterile marriages are due alone to the female. Women are constantly seen at the Clinic who have come alone several hundred miles for correction of sterility. In them no explanation for the barren marriage can be found. A few of them can be prevailed upon to send for the husband, and in many instances we find the answer in an impotent seminal secretion. About one-half of the sterility problems brought to the Mayo Clinic are due to fault in the male.

Perversion of the vaginal secretion has long been deemed one of the causes for sterile marriages. The means usually employed to measure the acidity is litmus paper. Obviously, the degree of acidity cannot be determined by this method. We are now, in conjunction with Magath, working to develop a satisfactory method of determining the relation between the acidity of the vaginal secretion, and the activity of the spermatozoa seen in the post-coital specimens.

There is no doubt that tubal inflation (transuterine pneumoperitoneum) is an important and practical addition to our armamentarium for the diagnosis of the etiology of sterility in women. If reasonable care is exercised in the selection of cases, no untoward results may be expected from the inflation. In none of the patients who have been subjected to this test in the Mayo Clinic have complications arisen as the result of its employment.

We are not prepared to make, as yet, a definite statement concerning the therapeutic effect of tubal inflation. In a certain number of patients, occluded tubes have been opened by this method, in some of whom occlusion was the only factor which could be found to explain the failure to conceive. It would seem logical to expect pregnancy to occur in these patients.

In the case presented, the history was one rather commonly met with in sterile women, that of a low grade and apparently insignificant infection, following either abortion or delivery. It is not possible to demonstrate gross lesions in such patients, but with the inflation, the fallopian tubes are found to be closed. This type of case should, it seems to us, be subjected to at least six tubal inflations before operation is advised. In a few instances, with a similar history the tubes have apparently been opened with gas under pressure.



## IODIN IN THE TREATMENT OF GOITER\*

WILLIAM A. PLUMMER

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In this discussion of iodin in the treatment of goiter, I shall limit myself to a rather superficial survey of its use in the prevention and treatment of endemic goiter, and to a summary of the results which have been obtained in the preoperative treatment of patients having exophthalmic goiter. As a preliminary to the consideration of endemic goiter, it is well to review some of the theories of etiology. The toxic infective theory assumes the presence in the gastro-intestinal tract of specific bacteria, probably of the colon type, the toxic product of which harmfully affects the thyroid gland. McCarlson has been the principal exponent of this view. In 1851, Chatin stated that goiter was due to the absence of iodin in air, water, and food. Recently, evidence in support of the iodin deficiency theory has been accumulating rapidly. Outstanding in this respect are the prophylaxis among school children, and the extensive comparative investigations of the iodin content of food and water in goitrous and nongoitrous regions. The Michigan Department of Health has made an extensive survey of the iodin content of the waters in Michigan, and a parallel investigation of the school children of the state for the incidence of goiter, it was found that the percentage of goiter varied inversely with the iodin content of the water supply. Fellenberg in Switzerland, and McClendon and Hathaway in this country, have shown that food, as well as water from goitrous regions contains less iodin than that from districts in which goiter is infrequent. H. S. Plummer has suggested that in certain individuals the development of goiter may be favored by an interference in the absorption of iodin.

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from the gastro-intestinal tract. The lack of uniformity in the results obtained from the oral administration of thyrovin or desiccated thyroid suggests the plausibility of this theory. In some cases 5 mg or more of thyrovin, or 20 gr of desiccated thyroid, may be given daily over an indefinite period without producing an appreciable increase in metabolic rate. That this occasional lack of response following the oral administration of 5 mg of thyrovin or an equivalent amount of desiccated thyroid, is due to incomplete absorption from the *gastro-intestinal tract*, is indicated by the fact that when thyrovin is given intravenously in such refractive cases a definite quantitative reaction is obtained from a much smaller daily dose. It is possible that bacterial action in the *gastro-intestinal tract* may interfere with the absorption of iodin as well as thyrovin or desiccated thyroid.

The first work in prophylaxis which was started between 1860 and 1870 in the schools of certain departments of France, was not well controlled, it was carried on in schools in which a majority of the children had already become afflicted with goiter, and following the occasional reports of resulting hyperthyroidism, it soon fell into disrepute. The next important movement was that of Marine and Kimball in the schools of Akron, Ohio, and was the culmination of investigations which Marine and Lenhart had been carrying on for a number of years. In the schools of Akron, 4 gm or 4,000 mg of sodium iodid were given in divided doses to each child during the school year. There were two periods of administration, each of ten days' duration. As a result of the campaign, goiter has been practically eliminated from the schools of that city. It may be due to the peculiar characteristics of thyroxin that these small quantities of iodin suffice to meet the demands of the thyroid gland. So far as we know at present, thyrovin is the only physiologically active substance secreted by the normal thyroid gland. In controlling the rate of energy transformation in the cells of the body, thyrovin acts as a catalytic agent. The following figures, although only approximately correct, further emphasize the small quantities of iodin necessary for prophyl-

axis When given intravenously, 0.75 mg of thyroxin, or less, is the daily amount necessary to maintain within normal limits the basal metabolic rate of an individual whose thyroid has been destroyed During the year this would amount to 270+ mg of thyroxin or 160+ mg of iodin It is also possible that the thyroid gland works a further economy by re-absorbing the iodin from the worn-out thyroxin molecule The 160+ mg of iodin should be amply supplied by the prevalent method of giving 10 mg of sodium iodid or iodostatin tablets once a week for a period of forty weeks Whether iodin in deficient areas should be reinforced by addition of the drug to the water supply, table salt, or by individual administration, is still a moot question

In discussing the treatment of simple goiter, the diffuse colloid enlargement common to the adolescent period is first considered For many years following Coindet's work in 1820, iodin was universally used, but more recently desiccated thyroid or thyroxin have often been substituted in the treatment of this type of goiter Iodin differs from thyroxin or desiccated thyroid in its mode of action When iodin in excess of the usual amount enters the circulation, it is picked up by the goitrous thyroid and probably facilitates the production of the thyroxin necessary to meet the demands of the body On the other hand, when thyroxin in quantities sufficient to meet these demands is injected directly into the circulation, the goitrous thyroid temporarily becomes an unnecessary organ In either case the stimulus on the gland becomes less, the blood supply is automatically reduced, and partial absorption of the colloid takes place After an abnormal amount of colloid has been deposited, many thyroid glands seem to be unable to utilize iodin satisfactorily, even though supplied in sufficient quantity, and absorption of the colloid only occurs after the gland has been put at complete rest by the administration of the necessary desiccated thyroid or thyroxin

The basal metabolic rate of the majority of patients having diffuse colloid goiters of adolescence, is below the average normal The basal metabolic rate may be as low as -18 Those

patients usually seem to be in good health, and have no complaints other than a slight local sense of pressure, and the objectionable appearance of the goiter. On more careful analysis, however, one notices an unusually dry skin, a peach and cream complexion, and lack of energy, all of which suggest a mild hypothyroidism. That the thyroid gland is being unusually stimulated in these cases is evidenced by its marked vascularity. Bruits and thrills can often be detected in the enlarged superior thyroid arteries, and occasionally the vessels can be easily palpated. When 5 or 10 mg. of thyroxin are injected intravenously, or an equivalent dose of desiccated thyroid is given by mouth, if it is absorbed a definite reaction takes place in all cases in from twenty-four to thirty-six hours. The bruits and thrills in the superior thyroid arteries disappear, and the gland may lose one-third of its volume. If, following the initial dose, sufficient thyroxin or desiccated thyroid is given by mouth to maintain the basal metabolic rate at normal or slightly above, large goiters of this type may become barely palpable in from two to twelve weeks. Desiccated thyroid is usually absorbed more readily than thyroxin, and it is impractical to administer thyroxin intravenously. The daily dose of desiccated thyroid required to hold the basal metabolic rate at normal varies within wide limits. It should be controlled by basal metabolic rate determinations. Adenomatous nodules scattered throughout the gland may render the treatment ineffectual. The larger the gland and the older the patient, the more likelihood there is of adenomatous tissue being present. In a patient more than twenty years of age, it is rather unusual to find a pure colloid goiter which is sufficiently large to be of significance. In fact, the treatment of simple goiter in patients who have passed the second decade in most instances resolves itself into the treatment of adenomatous goiter. If the goiter contains adenomatous tissue, the administration of iodin, especially after the age of adolescence, is not a safe procedure. There is conclusive evidence that iodin given to reduce an adenomatous goiter may initiate a hyperthyroidism which persists after the drug is discontinued. This develops most frequently after several weeks'

or months' administration of massive doses contained in preparations distributed by advertising goiter specialists. However, smaller amounts given over a longer period may also initiate hyperthyroidism. It is improbable that the minute quantities of iodin ingested from an iodized salt or water supply would be sufficient to initiate a hyperthyroidism in a patient having an adenomatous goiter. Desiccated thyroid, when administered in sufficient quantity, will produce a hyperthyroidism, but unlike iodin, does not apparently cause the adenomatous tissue to hyperfunction, and when discontinued, the symptoms gradually subside. However, such treatment seldom reduces the size of an adenomatous goiter sufficiently to satisfy the patient, and it does not lessen the danger of hyperthyroidism developing later. Desiccated thyroid may be indicated in the rare case in which the basal metabolic rate is below normal. This is especially true when the adenomatous tissue is growing rapidly in remnants of gland left from a previous operation, and represents all the functioning thyroid tissue which remains. In older patients, especially those past twenty-five years, an adenomatous goiter of any considerable size, even though associated with much diffuse colloid enlargement, requires surgical treatment.

In the past, many physicians have administered iodin in cases of exophthalmic goiter, evidently without grasping the spectacular results that may follow. Those who have at first noted beneficial results have, as a rule, ultimately condemned its use. In March, 1922, H. S. Plummer introduced the use of iodin in the treatment of exophthalmic goiter. Its trial was based on the observations and hypotheses briefly reviewed in the following paragraphs.

The thyroid under normal conditions delivers thyroxin into the circulation. This agent hastens metabolism, maintaining a basal metabolic rate of approximately 39 calories each hour for each square meter of body surface. An increase above normal in the amount of thyroxin in the tissues of the body elevates the basal metabolism, the resulting status being known as hyperthyroidism. The phenomena observed in a person, made hy-

perthyroid by the administration of thyroxin, are all that might be anticipated from an elevation of the basal metabolism. The clinical syndrome in hyperfunctioning adenomatous goiter is the same, so far as can be determined, as the one following the administration of thyroxin.

In cases of exophthalmic goiter the thyroid is intensively stimulated. This stimulation causes the delivery of thyroxin in excess of normal, and an abnormal product that gives rise to that part of the exophthalmic goiter syndrome which characterizes the disease. The more characteristic of these phenomena may be grouped under the eye findings, and the manifestation of a toxin acting on the nervous system.

The syndrome of exophthalmic goiter varies primarily in different cases, and from time to time in the same case, with the total and relative amounts of the two products namely, thyroxin and the abnormal product causing the eye findings, and peculiar nervous manifestations. The syndrome also varies with many other secondary factors, among which may be mentioned the duration of action of the two agents, and those that may be grouped under the heading, "personality of the patient." The total and relative amounts of the two products vary with the intensity of stimulation of the thyroid, the truing of the gland and the amount of iodin available. With alternate remissions and exacerbations in the intensity of stimulation, the thyroid becomes capable of delivering a relatively large proportion of the normal product under a given degree of stimulation.

The majority of deaths from exophthalmic goiter occur when the amount of the abnormal product in the tissues is relatively high, and under either one of two conditions: first, in a crisis, and second, from some infectious process, such as pneumonia, endocarditis, and suppurative cholecystitis, which has its inception from the lowering of resistance in a crisis or near-crisis period. Following this theory, it was anticipated that the administration of iodin in sufficient quantities would markedly or absolutely control the portion of the syndrome due to the agent causing the more characteristic phenomena of the disease.

This would mean the elimination of the nervous phenomena, the further development of eye conditions, and the majority of postoperative as well as preoperative deaths. The results which have followed the administration of iodin indicate that iodin nearly or completely controls that portion of the syndrome due to the abnormal product.

In the Mayo Clinic we now give 10 minimis of Lugol's solution as a routine three times a day for at least seven days previous to a thyroidectomy. The solution is administered for a longer period to patients who have been in a particularly bad condition, and are at the end of this period rapidly improving. To patients in a crisis or near-crisis, 50 minimis are given during the first two or three hours, by mouth if it can be retained, otherwise by rectum. If the patient is in a crisis, this is followed by 50 minimis during the following forenoon. To the patients having so-called postoperative recurrences that can be controlled are given 10 minimis of the solution daily over an indefinite period. This period is generally determined by stopping the iodin at intervals of a few weeks, and noting the patient's condition at the end of ten days. If there is any recurrence of hyperthyroidism, the administration of iodin is again resumed.

The results may be briefly stated as follows. The symptoms characteristic of the disease, as distinguished from the symptoms that might result from the administration of thyroxin, disappear in from one to ten days. This includes the "stare" but not the exophthalmus, which in a sense remains a deformity. The crisis is always controlled within a few hours. As a rule, the patient can take food within twenty-four hours. For many years in the Mayo Clinic there has been an average of about fifteen deaths a year in cases of exophthalmic goiter not treated surgically. Since the introduction of the use of iodin this mortality has been rapidly reduced. From January 1 to September 1, 1924, from 600 to 700 new cases of exophthalmic goiter were observed in the Clinic. During this period there were no medical deaths. The operative mortality has been reduced 2 per cent or more by the administration of iodin. Preliminary ligations have, to a large extent, been eliminated from the treatment. The surgical mortality, by case, this year is 0.6 per cent.



## FOUR CASES OF HEMORRHAGIC PURPURA WITH SPLENECTOMY

HERBERT Z. GIFFIN

It is very unusual for us to have under observation at one time four patients with hemorrhagic purpura. Moreover, these four patients have recently been splenectomized with very striking results. Our series of splenectomies for hemorrhagic purpura now numbers eight. Our first case was mentioned in the discussion of a paper by Brill and Rosenthal, in 1923, and was also referred to in the Medical Clinics of North America in 1923. The patient has been well for eighteen months. A report of the first four cases together with a review of the literature has recently been submitted for publication elsewhere. Brill and Rosenthal first focused the attention of physicians in this country on the remarkable results that had been obtained abroad following splenectomy for hemorrhagic purpura. Their papers are of special interest and importance.

Case 1.—The first case I wish to discuss is that of a man, aged thirty-two, who came to the Clinic August 28, 1924. A history of hemophilia in the family was not obtained. The patient had apparently been well until two years before, when he began to have purpuric areas on the slightest injury. Often these areas spread widely before beginning to clear up. Petechiae appeared, and scratches would bleed for an exceedingly long time. The condition gradually became worse until in September, 1923, considerable bleeding occurred for several weeks. There were hemorrhages from scratches on the scalp, hemorrhages into the sclerae, and bleeding from the nose and gums. Blood was found in the urine and in the stools. The hemorrhages were not excessive, and the patient was not markedly anemic, but transfusions were resorted to in an endeavor to decrease the hemorrhagic tendency. The patient gradually became better during the following six months, and from April 1 to the time of his examination in August, he had been troubled chiefly with purpuric areas, sometimes accompanied by subcutaneous hemorrhages forming nodules under the skin, petechiae, rather free bleeding from scratches and cuts, and bleeding from the gums on brushing the teeth. A mild degree

of arthritic pain was present, but there was no actual inflammatory reaction around the joints.

The patient appeared well nourished, strong, and active. Petechiae were present over the shoulders and the extremities. In various parts of the body were large purpuric areas. One subcutaneous nodule could be felt under a purpuric area in the calf of the left leg. The spleen was barely palpable with the patient lying on the right side. The patient's blood count August 28 was as follows: hemoglobin 83 per cent, erythrocytes 4,170,000, leukocytes 5,800. The differential count showed nothing of apparent significance. The platelets numbered 36,000, the coagulation time by the Boggs method was six minutes, the bleeding time fifteen minutes, the coagulation time by the Lee method was twelve minutes, the calcium time sixteen minutes, and prothrombin time was slightly prolonged. Retractility of the clot was absent at the end of two hours, and a tourniquet test was positive. A dental x-ray was negative and the tonsils were small, but slightly infected. Wassermann reaction, urinalysis, and examination of the eye grounds were negative.

Splenectomy was performed on October 8 by C. H. Mayo. The spleen weighed only 164 gm., although it had been palpable preceding operation. Convalescence was entirely satisfactory. By the sixth day the platelet count had risen to 684,000 and the bleeding time was five minutes. On the tenth day the platelet count was 674,000, and the bleeding time was three minutes. Slight retraction of the clot occurred in forty minutes. On the eleventh day the platelet count reached its highest level, 816,000 and the bleeding time was two and one-half minutes. October 27 twenty days after the operation the hemoglobin was 62 per cent, erythrocytes numbered 3,690,000, and leukocytes 15,200, the differential count was not significant, aside from a slight rise in the percentage of polymorphonucleate (79 per cent). The platelet count had become reduced to 188,000, the coagulation time by the Boggs method was eleven minutes, by the Lee method seven and one-half minutes, the calcium time was ten and one-half minutes, the bleeding time two minutes, and the prothrombin time was normal. Retractility of the clot was absent at one hour, but present at the time of the next reading sixteen hours. The patient has had no bleeding since operation and no petechiae or purpuric areas have appeared. Before operation the patient complained of aching in the joints; this has disappeared.

*Comment*—Case 1 is an example of the mild type and chronic form of hemorrhagic purpura. It differs from the other cases I have seen in the occurrence of massive purpuric areas associated with subcutaneous hematomas, the fact that these hematomas have not reappeared since splenectomy is of special interest. It is also important to know that the mild type of the disease is apparently followed by a satisfactory result as are the more severe ones. The spleen was palpable with the patient lying on

the right side, but was found to weigh only 164 gm. The low platelet count, the long bleeding time, and the irtractability of the clot, together with a positive tourniquet test, constitute the chief diagnostic features with respect to coagulation. It will be noted that the highest platelet count was observed between the sixth and tenth days following operation, when the platelet count was 816,000. This patient complained before operation of arthritic pains, but his joints never showed inflammatory reaction, these pains were almost immediately relieved after splenectomy.

Case 2.—A girl, aged eleven, came to the Clinic September 22, 1924. She was referred by J. S. Weingart of Des Moines, Iowa. The family history was not definitely indicative of hemophilia, although the father's aunt had had epistaxis as a child, and two cousins, the children of a paternal uncle, had bled considerably, one after tonsillectomy and the other after appendectomy. The patient had been well until the age of five and one-half years, when she was sent home from school with an eruption which at the time was thought to be measles, but which proved to be petechial hemorrhages, and from that time on she was bothered with petechiae, purpura, and occasionally epistaxis, at times requiring packing. There was bleeding into the sclera several times. The gums had bled easily ever since the onset of the trouble. At the age of six, following a fall, the patient bled rather freely from the vagina for three or four days, and at the age of seven, bleeding from the bowel was noted for one day. During the few weeks directly preceding admission excessive recurrent nosebleed had been so severe that marked anemia had developed. The slightest exertion brought on hemorrhage and occasional attacks of fever, at times reaching 101°. Menstruation had not yet become established.

At the time of admission the patient's hemoglobin was 38 per cent, the erythrocytes numbered 3,560,000, and leukocytes 8,000. Nothing of significance was noted in the differential count aside from a rather high percentage of neutrophils (83 per cent). The platelet count was 54,000, the bleeding time was ten minutes, the coagulation time, by the Boggs method, seven and one-half minutes, and by the Lee method ten minutes. The calcium time was twenty-one minutes. A tourniquet test was positive, petechiae appearing in one and one-half minutes. Marked prolongation of the prothrombin time was noted, and retractility of the clot did not occur at the end of three hours. An estimation of the fragility of the erythrocytes showed evidence of increased resistance, and a Wassermann reaction was negative. On absolute quiet in bed severe hemorrhages ceased, and the blood count improved on the administration of Blaud's pills and Fowler's solution, transfusions were not necessary. Two weeks after admission the hemoglobin was 45 per cent, and the erythrocytes numbered 4,330,000. Many platelet counts were made, and these were for the most part between 54,000 and 68,000.

On two occasions there was an increase of the platelet count to approximately 180,000. The spleen was easily palpable and somewhat hard.

Splenectomy was performed October 10 by C. H. Mayo. The spleen weighed 202 gm., and was definitely enlarged, especially in consideration of the weight and age of the patient. Convalescence occurred without complications. The third day following operation the platelet count was 643,000, and the bleeding time had become reduced to three and one-half minutes. By the fifth day following operation the platelet count was 470,000, the bleeding time was three minutes, the coagulation time by the Lee method six and one-half minutes, the calcium time six and one-half minutes, the prothrombin time was normal, and there was slight retractility of the clot in twenty minutes. The highest platelet count of 780,000 occurred on the sixth day. On October 27, eighteen days after operation, the hemoglobin was 47 per cent, the erythrocytes numbered 3,950,000, and the leukocytes 10,400. Although the platelet count had become reduced to 88,000, the bleeding time was only two minutes. Coagulation time by the Boggs method was four minutes, by the Lee method seven and one-half minutes, the calcium time was seven and one-half minutes, and the prothrombin time was normal. The clot showed slight retractility at two hours and at three hours, the next reading was at twenty hours, when marked retraction was noted. The patient has had no fresh hemorrhage since the operation, and all former purpura areas have disappeared. Her general condition is very satisfactory.

*Comment*—This patient, aged eleven years, is the youngest of the group. Another girl of eleven was operated on last March. The youth of these two patients did not seem to influence the result obtained. The duration of the disease had been approximately five years and severe anemia had been caused by excessive epistaxis. The occurrence of attacks of fever is also of interest. Absolute rest in bed and, as nearly as possible, absolute quiet in bed seemed to be more effective in controlling the hemorrhage than coagulants or other medicinal measures. It will be observed that the highest platelet count occurred on the sixth day following operation (780,000), and that the count later became reduced to 88,000, without however, a recurrence of bleeding.

*Case 3*—A girl, aged fifteen, was examined September 24, 1921. A history of hemophilia or hemorrhagic tendency in the family was not obtained. Petechiae and purpura on slight injury had made their appearance at the age of five. These had gradually become more pronounced. Since menstruation had become established two years previously, the petechiae disappeared during the flow. Epistaxis had occasionally occurred, in three or four hours at a time. Bleeding from the gums had never been

troublesome. The patient began to menstruate at the age of thirteen, and flowed at intervals of from four to six weeks, with a duration of from four to as long as thirty days. At the time of the onset of menstruation she was confined to the hospital for five weeks on account of the excessive loss of blood, and was at that time given several transfusions. All of her periods were very profuse, although some were of short duration. Six months preceding admission menstruation was again excessive, and hospital care and transfusions became necessary.

At the time of admission she had had continuous menstruation for four weeks. Her hemoglobin was 14 per cent, the erythrocytes numbered 1,370,000, and the leukocytes 7,200. A differential count showed nothing of importance. The platelet count was 42,000, retraction of the clot was not present at the end of twenty-four hours. The bleeding time was six minutes, coagulation time by the Boggs method was seven minutes, and by the Lee method seven minutes. The calcium time was also seven minutes, and the prothrombin time was slightly prolonged. The tourniquet test was positive, petechiae appearing in two and one-half minutes. One transfusion of 500 cc was given by the citrate method, and improvement was very rapid. By October 13, approximately three weeks after admission, the hemoglobin was 45 per cent, and the erythrocytes numbered 3,760,000. The platelet count for the first two days after admission was in the neighborhood of 40,000, after transfusion the platelet count jumped to 212,000, to drop the next day to 28,000. Thereafter, there was a considerable variation in the platelet count, estimations varying from 42,000 to 166,000, the count most of the time being slightly above or below 100,000. The general physical examination disclosed nothing of significance aside from the features of hemorrhagic purpura. The patient was well nourished. The spleen was easily palpable, and somewhat hard. Pelvic examination did not reveal evidence of any pathologic condition which might account for the metrorrhagia.

Splenectomy was performed October 16, 1924, by W. J. Mayo. The spleen weighed only 125 gm., but was estimated at the time of operation to be three to four times normal size, this discrepancy was probably due to the fact that the organ was distended with an abnormally large amount of blood. Convalescence was uneventful. No bleeding whatever of any type has occurred since the operation, and the purpuric areas and petechiae have entirely disappeared. On the third day after operation the platelet count was 64,000, on the fifth day the platelet count had risen to 516,000, but the bleeding time was still prolonged (seven and one-half minutes), and retraction of the clot did not occur at the end of six hours. On the ninth day the platelet count was 105,000, and the bleeding time three and one-half minutes, coagulation time by the Boggs method was eight minutes, slight retraction of the clot was present at the end of two hours. On the fifteenth day the platelet count was 408,000, the bleeding time six and one-half minutes, and clot retraction had begun at four hours, but was not satisfactory at the end of twenty-four hours.

*Comment*—This patient entered the hospital with extreme anemia, the hemoglobin was 14 per cent, and the erythrocytes

numbered 1,370,000. One transfusion by the citrate method was sufficient apparently to initiate rapid improvement. The excessive bleeding in this instance was uterine, as is so often the case in this disease after menstruation has become established. In fact, in all instances of menorrhagia at puberty, or shortly afterward, an examination should be made for the features of hemorrhagic purpura. It may be noted that satisfactory clot retraction was not present on the fifteenth day after splenectomy. We have as yet no accurate data on the exact period following splenectomy at which clot retraction becomes normal.

**Case 4**—A young lady, aged eighteen, came to the Clinic January 30, 1920. A family history of hemorrhagic disease was not obtained. Menstruation had begun at the age of thirteen and was irregular and profuse. The intervals between menstrual periods varied from one to three months. At the age of thirteen she bled excessively, and at one time bled for four weeks, necessitating absolute rest and picks. At the age of sixteen she was again confined to bed on account of menorrhagia, and from then until admission frequent periods of complete disability were caused by loss of blood. The patient had had nosebleed occasionally as a child, and bleeding from the gums had been more or less troublesome for one year. Purpuric areas and petechial eruptions had been present more or less constantly for several years.

The patient was well nourished, but extremely anemic. The hemoglobin was 15 per cent, the erythrocytes numbered 1,800,000, and the leukocytes 3,400. A differential count showed polymorphonuclear neutrophils 69, small lymphocytes 24.5, large lymphocytes 5, eosinophils 1, and basophils 0.5, anisocytosis moderate, poikilocytosis moderate, and polychromatophilia slight. The platelet count was 196,000 (possibly not accurate). The bleeding time was four minutes, coagulation time by the Boggs method was seven minutes and by the Lee method eight minutes, and the prothrombin time was not prolonged. An examination of the pelvis did not reveal definite evidence of any pathologic condition, although the cervix was somewhat soft and relaxed. After a series of four transfusions by the citrate method the blood count became normal. By April 12, the hemoglobin was 72 per cent, and the erythrocytes numbered 4,610,000. A curettage was performed April 21, 1920. After this time she had had no serious difficulty with excessive menstruation, although at times the flow was quite profuse. In December, 1920, the hemoglobin was 71 per cent, the erythrocytes numbered 4,250,000, and the leukocytes 7,500. The platelet count was 70,000, the coagulation time by the Boggs method ten minutes, and the bleeding time was more than sixty minutes. Two years later, February 2, 1922, the platelet count was 76,000. The patient at this time continued to have petechiae, purpuric areas, and bleeding from the gums on slight trauma; otherwise she seemed to be healthy. She was examined again in September, 1923, at which time there was a per-

sistently low platelet count, varying from 46,000 to 72,000, and the bleeding time had become prolonged to seven and one-half minutes. The hemorrhagic tendency was troublesome and the patient was at times partially disabled by the recurrent purpura and bleeding. A tonsillectomy was performed November 30, 1923, followed by hemorrhage and hematomas, necessitating a stay in the hospital for about two weeks. An infected tooth was extracted in March, 1924. The elimination of these foci did not, however, bring about improvement. During the year 1924, a great many blood counts and estimations were made of the coagulation factors. The platelet count usually fluctuated between 22,000 and 72,000. There was one period during which the count became increased for a period of two weeks, and varied from 100,000 to 206,000. The coagulation time by the Boggs method varied from five to ten minutes, it was usually less than six minutes. The bleeding time fluctuated from three and one-half to twenty-four minutes, and was usually in excess of five minutes. It is not noted that the spleen was enlarged at any time. Frequent unsuccessful efforts were made during 1924 to palpate the spleen. I am not certain, however, that it was not palpable during a period of excessive bleeding in 1920.

Splenectomy was performed October 23, 1924 (E. S. Judd), over four years after the first examination. The spleen was not enlarged, and weighed, after losing its blood, only 92 gm. The gallbladder and the liver were apparently normal. There was some oozing from the abdominal wound when the incision was made, but the wound was quite dry at closure. The convalescence was entirely uneventful. The temperature was never higher than 99.5°. Four hours after operation the platelet count was 200,000, on the following day it was 320,000, and by the ninth day, 840,000. On the fifth day slight retraction of the clot was present in thirty minutes, the clot was not firmly retracted, however, in twenty-four hours. Petechiae and purpuric areas disappeared rapidly after operation, and bleeding from the gums, which had been present continuously for five years at the slightest trauma, ceased. The patient has been well since then.

*Comment*—This case is of special interest because of the fact that for a period of at least five years preceding splenectomy the hemorrhagic purpura had been of a very mild grade. Preceding that time there had been excessive menstruation and severe anemia. Despite the mild type of the disease, the result following operation has been similar to that in the more active and more severe cases. It is also especially important to know that removal of a small spleen, weighing only 92 gm, is followed by the same result as the removal of an enlarged spleen. The spleen was weighed, however, some time following operation.

## DISCUSSION

These four patients illustrate very satisfactorily the features of hemorrhagic purpura, both in the severe and in the mild types of the disease. Splenectomy has been surprisingly effective in causing a disappearance of almost all of the features of the disease. The improvement following operation is just as prompt and much more spectacular than improvement following splenectomy for hemolytic jaundice. It is necessary to differentiate hemorrhagic purpura from hemophilia, acute aplastic anemia, certain forms of acute leukemia with hemorrhagic manifestations, cases of multiple telangiectases with secondary bleeding, and a certain group of cases which might be termed familial epistaxis. Very rarely a case is seen in which characteristics do not conform definitely either to hemophilia or to hemorrhagic purpura. I have in mind a patient who repeatedly suffered from excessive menstruation, who manifested some of the coagulation features of hemorrhagic purpura, and in whose family there was definite evidence of hemorrhagic diathesis. I have seen recently another patient in whom all of the features of hemorrhagic purpura were present with the exception of the low platelet count. In one case of acute aplastic anemia, with features of hemorrhagic purpura from the stand point of the coagulation tests, splenectomy was performed in the Clinic without altering the course of the disease. In this instance a consistently low leukocyte count was present and the development of anemia preceded the onset of hemorrhages. In this differentiation of acute aplastic anemia with hemorrhagic manifestations, and hemorrhagic purpura the persistent leukopenia may be of very great importance. The reduced number of platelets, the long bleeding time, the absence of retractility of the clot, and the presence of petechiae on the application of a tourniquet, are the features which will usually clearly differentiate hemorrhagic purpura from any of the other diseases mentioned. The absence of a family history of hemophilia and the absence of hemophilic joints are also of especial importance in the diagnosis.

The spleen was palpable at the time of operation in only

two of these four patients. One of the spleens seemed to be considerably enlarged. The weights were respectively 202, 164, 125, and 92 gm. The organs were weighed, however, after the loss of considerable blood, and there is a discrepancy between the weight of the spleen and its apparent size at the time of examination. This would seem to indicate that the organ is filled, in this disease with an abnormally large amount of blood.

Our observations in general suggest that the average level of the platelet count is low before operation, with an occasional rise to normal, and that on the other hand, the platelet level after operation is high, with an occasional drop below 100,000. There seems to be considerable evidence which indicates that platelet destruction may be a fundamental factor in the disease. The very rapid increase in the number of platelets following splenectomy accompanied by the immediate cessation of hemorrhages, could best be explained by the immediate cessation of the excessive destruction of platelets. Results following splenectomy are comparable to those obtained in hemolytic jaundice, which is essentially a disease of hemolysis, and in which an abnormality of the red cells is probably fundamental. Similarly an abnormality of the platelets seems to be fundamental in hemorrhagic purpura.

As a point of departure in the enumeration of the platelets in disease, I would like to call attention to the observations of Holloway and Blackford. They found that the platelet counts on blood from the splenic vein were not normally lower than on that of the splenic artery and that counts on venous blood, in general, were slightly higher than those on arterial.\*

\* Am Jour Med Sc, 1924, clxxviii, 723-728



# THREE CASES OF PERNICIOUS ANEMIA AND DIABETES MELLITUS WITH A NOTE ON THE APPARENT INEFFECTIVENESS OF INSULIN IN THE PRESENCE OF A PROFOUND ANEMIA

S FRANKLIN ADAMS

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These cases are reported because of the unusual occurrence of the two diseases together, and because of the apparent decreased ability of insulin to lower the blood sugar in the presence of a profound anemia

## REPORT OF CASES

**Case 1** —A woman, aged forty-five years, came to the Clinic October 26, 1910, because of disturbance of vision. A diagnosis of presbyopia was made. She was seen again August 15, 1912, at which time she had an indefinite anemia. Part of the records of the case from 1912 to 1918 were lost, but the blood counts, which were made up to February, 1918, may be noted in Table 1. October 3, 1919, she returned for examination. The findings at this time were somewhat suggestive of splenic anemia. There is a note on this date to the effect that the patient had been seen at intervals of a few months during the past eight years, and that her spleen had always been palpable. She had complained at times of weakness and a slight sense of discomfort in the splenic area.

March 21, 1923 she reappeared at the Clinic. During the previous November the patient had had an illness "much like influenza". She had considerable diarrhea, and hemorrhoids had become troublesome and had bled. During the last year she had had slight prolapse of the uterus, particularly when she was on her feet a great deal, or if she lifted heavy objects. She had passed through eighteen pregnancies, but no hemorrhages had occurred. She had had attacks of asthmatic bronchitis when she became chilled.

Examination revealed enlarged spleen, heart and lungs normal, uterus prolapsed and retroverted, a moderate degree of cystocele and rectocele, protruding hemorrhoids, evidence of pruritus, skin around the vulva softened and whitened, and scratch dermatitis. A single specimen of urine contained 8.2 per cent sugar, which was the first suggestion of diabetes. With the exception of the pruritus, there had been no sign of the disease. The blood

sugar was 0.317 mg, the plasma carbon dioxid capacity 53 volumes per cent. The blood Wassermann reaction was negative. A hemorrhoidectomy was performed March 21, with transsacral anesthesia. For several days before the operation, the patient was studied from the diabetic standpoint. On a diet of 17 gm of carbohydrate, 37 gm of protein, and 118 gm of fat, she promptly desugared. For the four days immediately preceding operation, her carbohydrate allowance was raised to insure adequate glycogen storage. At this time her blood count was normal (Table 1). Following the operation a mixture of food was given from which the concentrated sweets and starches were omitted. The patient excreted 39 and 66 gm of sugar on the third and fourth days after the hemorrhoidectomy, but, on withdrawal of some of the carbohydrate, the urine became free from sugar. Although insulin was available at this time, it did not seem necessary to employ it because of the mildness of the patient's diabetes. When she returned home she continued to omit concentrated sweet foods from her diet, and frequent examinations of the urine during this period did not reveal more than an occasional trace of sugar.

January 28, 1924, the patient again came to the Clinic. She had felt very well until about six weeks before. During the preceding month she had lost strength. She complained of marked exhaustion on the slightest exertion, numbness and tingling of the finger-tips, and "the soles of her feet did not feel natural." She had noticed edema of the feet and legs during the last few weeks. She had slight vertigo, tinnitus aurium, slight nocturia, slight polydipsia, and polyuria. Her weight was 129 pounds. Her systolic blood pressure was 128, the diastolic 64, the pulse rate was 105 and the temperature 99.6°. Her skin and mucous membrane were very pale, all of her teeth had been extracted. The heart rate was moderately rapid, and the sounds, distant. The lungs give evidence of slight emphysema. The spleen was moderately enlarged and movable. There was moderate edema of the feet and legs. The blood count at this time showed considerable anemia (Table 1). The blood sugar was 0.410 mg for each 100 c.c. The urine contained 3.5 per cent sugar. The patient was sent immediately to the hospital. She was started on a diet of 100 gm of carbohydrate, 80 gm of protein, and 198 gm of fat, which was given to afford adequate nourishment. This mixture of food was devised to contain 20 mg of iron, and on this diet it seemed necessary to use 10 units of insulin three times a day in order to keep the urine sugar-free, although, toward the end of the patient's stay in the hospital, the insulin was gradually withdrawn and finally discontinued entirely. The diet remained unchanged throughout and her urine was continually free from sugar. The blood sugar fell to 271 mg and remained at about this level during the five weeks spent in the hospital. The hemoglobin was between 30 and 35 per cent, the erythrocytes between 1,410,000 and 2,270,000. The leukocytes did not exceed 4,000. The urine was negative for urobilin and urobilinogen. The stools were examined for parasites and ova on eight occasions, but were negative each time. No free hydrochloric acid was found in the stomach. Transfusions of 500 c.c. of blood were given February 6, and February 27, with a mild reaction following the second transfusion. The patient was in Group 4.

	August 15 1912	June 21, 1917	July 10, 1917	September 6, 1917	November 6, 1917	February 8, 1918	March 21 1923	April 12, 1923	January 28, 1924	February 18, 1924	March 2, 1924	April 14 1924
Hemoglobin (Dove) per cent	50	55	75	78	67	68	78	74	41	30	35	40
Erythrocytes (millions)	4.09	3.03	4.03	4.44	4.30	3.4	3.94	4.36	1.83	1.88	2.4	1.3
Color Index	0.6+	0.9+	0.9+	0.8+	0.7+	1.0	1.0	0.8	1.1+	0.8	0.7	1.5
Leukocytes	3,800	5,200	5,200	4,600	4,800	6,000	7,100	7,200	1,000	3,200		
Cells counted	100	200	300	300	300	300	300	300	200	200		
Small lymphocytes	31.3	42.5	35.0	34.7								
Large lymphocytes	1.7	3.5	4.3	7.0								
Neutrophils	62.0	50.0	58.0	52.7								
Eosinophils	1.0	2.5	2.3	4.3								
Basophils	1.0	1.3	0.3	1.3								
Myelocytes											1.5	
Normoblasts										2.0		
Anisocytosis		Slight	Slight							Moderate		
Poikilocytosis		Slight	Slight							Moderate		
Polychromatophilia										Slight		

APRIL 16, 1924 TREATMENT AND RESPONSE

Time	Laboratory data	Procedures
6:00 a.m.		Lost consciousness Saline enema, heat applied
7:30 a.m.	Blood sugar 0.400 mg Carbon dioxide plasma 15 volumes per cent	Insulin, 30 units subcutaneously
9:00 a.m.		Glucose, 10 gm intravenous injection, subcutaneous administration of normal salt solution started
11:00 a.m.		Digitalis 1 c.c.
12:00 m		50 units insulin Digitalis, 1 c.c. 30 gm soda in 1,000 c.c. normal salt solution, proctoclysis started
2:45 p.m.	Blood sugar, 0.403 mg Carbon dioxide plasma 27 volumes per cent	
3:45 p.m.	Blood sugar, 0.473 mg Carbon dioxide plasma 27 volumes per cent	30 units insulin
5:45 p.m.		100 units insulin, 15 gm soda
6:40 p.m.		Patient died

The neurologic examination revealed slight ataxia, absent reflexes in the lower extremities and abdomen, but active reflexes in the arms, lost vibration sensibility of the lower extremities and hips, impaired joint sense, Babinski of the right foot, and these findings, together with such subjective sensations as tingling finger tips and "rubber soles" led to a diagnosis in the Department of Neurology of subacute combined sclerosis. The usual medicinal treatment for pernicious anemia supplemented the other measures, and the patient was dismissed from the hospital March 4. During her hospital course, one of her daughters attended the dietetic classes conducted for diabetic patients and she was trained to assist in the care of her mother at home.

The patient's condition remained about the same until April 16, 1924, except that she became more anemic. She passed a comparatively normal day, on the fifteenth, but suddenly lost consciousness at 6:00 a.m. the following morning. There was an acetone odor to the breath, the extremities were cold, the heart tones were weak, rales could be heard at the base of both lungs, the respirations were of the Kussmaul type. She remained unconscious until death at 6:40 p.m. In Table 1 the treatment resorted to, and the evidences of the failure of the patient to respond to large doses of insulin are given.

*Autopsy findings.*—There was considerable emaciation, the spleen weighed 312 gm., its cut surface was brick red, the liver weighed 1,787 gm. the cut surface was yellowish, the stain for iron was positive. The pancreas weighed 68 gm. There was extreme fatty replacement. The parenchyma was dense and fibrous. The bone marrow was grayish red. A section of the liver revealed slight thickening of the capsule and a fairly marked periportal fibrosis, microscopically. The polygonal cells were faintly stained in areas. Moderate diffuse fatty changes were present. The sinusoids were not distinct and contained small amounts of a yellowish brown pigment. Much of the pigment was distinctly within the Kupffer cells. The iron stain showed this pigment to contain hemosiderin. In the pancreas (Fig. 188), there was marked atrophy of the acinar tissue certain areas contained one or two, surrounded by islands lying in a fibrous connective tissue bed with large spaces of loose fragmentary fibrous tissue, extended in every direction. In other areas there were groups of ducts with no acinar tissue between or around them, in still other areas small islands of acinar tissue in a loose connective tissue framework, and marked fatty changes. The islands had hyalosinibrinoid changes. In the bone marrow (Fig. 189) were a moderate number of megakaryocytes numerous normoblasts and eosinophilic. There was no evidence of its normal fatty structure.

*Case 2.*—Soon after observations had been completed in Case 1, a similar case was observed. The patient, a woman of fifty-eight years, came to the Clinic December 17, 1923. Ten years before, a doctor whom she consulted because of pruritis vulvae had found a girl in her room and told her to omit the obviously concentrated sweets and sweet foods from her diet. She did this and noticed no remarkable change in her health until two years before admission to the Clinic, when her mouth and tongue became sore. Two or three months before admission pain as well as loss of the hair in an affected area, and

Examination revealed an atrophic tongue, varicose veins, diminished vibratory sensibility in the lower extremities, and a positive Romberg sign. Her fasting blood sugar ranged from 230 to 160 mg for each 100 cc.

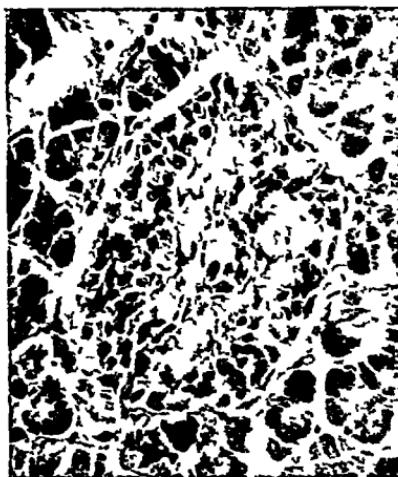


Fig 188—Marked atrophy of the acinar tissue

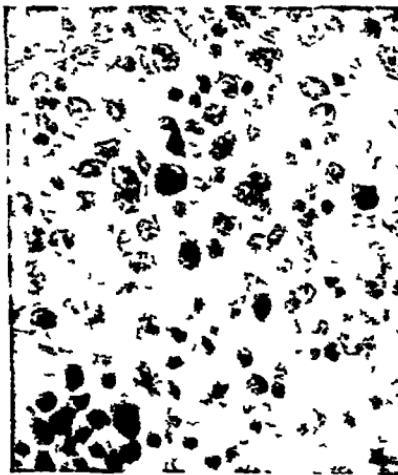


Fig 189—The bone-marrow, showing a moderate number of megaloblasts, and numerous normoblasts and eosinophils

The blood volume index was 1.3. The blood counts are given in Table 2. The blood Wassermann reaction was negative, gastric analysis indicated a total acidity of 12 and no free hydrochloric acid.

TABLE 2  
BLOOD FINDINGS IN CASE 2

	December 17, 1923	January 9, 1924	March 21, 1924	June 19, 1924	June 26, 1924	June 29, 1924
Hemoglobin (Dare), per cent	48	57	63	45	52	
Hemoglobin (grams)				11.3		
Erythrocytes (millions)	2,81	2,95	3,37	2,65	2,50	
Color index	0.8+	0.9+	0.9+	1.3+	1	
Leukocytes	3,100	5,800	3,700	11,200	3,400	
Cells counted	200	200		100	100	300
Small lymphocytes	69.0	30	55	58	69	45
Large lymphocytes	1.5	4.5	1		2	2
Neutrophils	24.5	60.5	37	42	27	47
Eosinophils	50	3.5	7		2	4
Basophils		1.5				
Anisocytosis		Moderate	Moderate	Moderate	Moderate	Moderate
Poikilocytosis		Moderate	Moderate	Moderate	Moderate	Moderate
Polychromatophilia		Slight	Slight	Moderate	Moderate	Moderate

In view of the apparent ineffectiveness of insulin in Case 1, this patient was given 20 units of insulin, after having fasted for eighteen hours (Fig 190). A few days later she was given 40 units of insulin under the same conditions. It is apparent that while insulin did reduce the blood sugar level, it took considerably more insulin to produce any effect, than would have been necessary under ordinary circumstances. In cases which we have observed in which 20 units of insulin have been given to patients with uncomplicated diabetes, and to a normal person, the blood sugar falls at the rate of about 1 mg each minute to the point where the curve begins to "flatten out." In this case, however, when 20 units of insulin were given, the blood sugar fell at the rate of approximately 1 mg every four minutes. With the 40 unit dose, the rate of fall was approximately 1 mg for every one and six tenths minutes.

Case 3.—A third case of pernicious anemia and diabetes mellitus has been observed at the Clinic, and was treated for the latter condition. This patient did not develop any of the manifestations of pernicious anemia until some time after his departure. The anemia was recognized by Dr C. I. Kemper of Denver, Colorado.

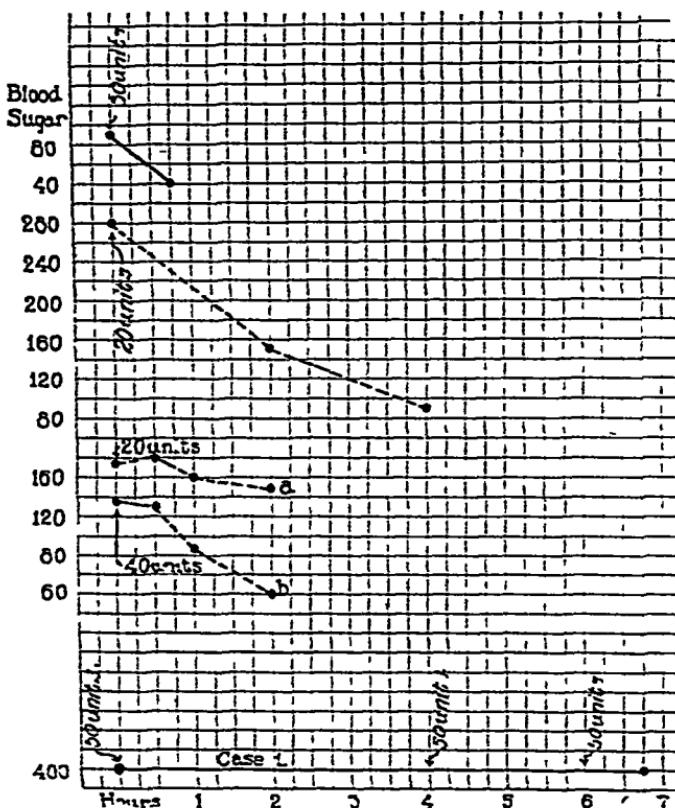


Fig. 190.—Curves showing the effect of insulin on the blood sugar in two cases of diabetes mellitus with pernicious anemia, as compared with the effect in an uncomplicated case of diabetes, and on a normal person

#### DISCUSSION

I have been able to find only one report of this combination of diseases. Parkinson,\* in 1910, observed a case of pernicious anemia terminating in acute diabetes. His patient, a man aged forty-nine years, died, apparently in diabetic coma, about eighteen months after the onset of the symptoms of pernicious anemia, and fifteen days after the onset of the symptoms of diabetes. The necropsy findings were characteristic of pernicious anemia, but the pancreas was normal. Parkinson mentions the

\* Parkinson, J. A case of pernicious anemia terminating in acute diabetes. *Lancet*, 1910, ii, 543-546

unusual occurrence of acute, severe diabetes in a middle-aged patient, and he believes that diabetes was the direct outcome of pernicious anemia in this case. This observation was made about fifteen years ago, and it might have appeared then that pernicious anemia would create a suitable metabolic state for the onset of diabetes. At present, however, this seems unlikely, chiefly because of the very rare association of the two diseases. During the last five years there have been approximately 1,000 patients at the Mayo Clinic with pernicious anemia, and approximately 2,000 with diabetes mellitus, and the cases reported here are the only ones in which there was a combination of the two diseases.

Insulin was apparently unable to reduce the blood sugar in two of these patients in the usual manner. The insulin used (Eli Lilly Company) had proved its effectiveness in other patients. Possibly the diminution of the oxygen supply, the result of anemia, was partly responsible for the apparent ineffectiveness of the insulin.

## THE BASAL METABOLIC RATE IN CASES OF PRIMARY CARDIAC DISEASE

WALTER M. BOOTHBY AND FREDRICK A. WILLIUS

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The first careful study of the basal metabolic rate of a group of patients with cardiac diseases was made by Peabody, Meyer and DuBois in the respiration calorimeter. Of eight patients with chronic endocardial valvular disease, four had a metabolism definitely above the normal variation (15 to 28 per cent), that of one patient with chronic myocarditis was 48 per cent above normal, a patient with adhesive pericarditis, and one with congenital heart disease had a normal metabolism, four of the six patients with hypertension, with or without clinical nephritis, had a basal metabolism 20 to 49 per cent above normal. These authors found no abnormal quotients, such as had invalidated some of the work of earlier writers, and the two methods of direct and indirect calorimetry were in satisfactory agreement. The elevation of metabolism which occurred in such a high proportion of their cases was attributed by them to dyspnea or restlessness. It must be remembered that prolonged periods of one or two hours, necessary in the respiration calorimeter, are not satisfactory for obtaining the true basal or standard metabolism, because it is almost impossible for the majority of sick patients to remain absolutely motionless throughout this length of time. For this reason short periods of approximately ten minutes are more satisfactory for the determination of the true basal metabolic rate.

Peabody, Wentworth and Barker have reported a very complete study on twenty-four patients with cardiac disease, in many instances the cardiac disease was complicated by chronic nephritis. In general there was little or no increase in metabolism in their Group 1 which comprised cases in which there was no dyspnea and the vital capacity was not seriously im-

paired. In contrast, the patients, classified in Group 2, who were really sick and incapacitated, and tended to be dyspneic on the slightest exertion, with a markedly decreased vital capacity, showed a definite tendency to an increase in the basal metabolic rate, this entire group averaged 13 per cent above normal, and six of the fourteen were above 20 per cent.

Boothby and Sandiford made two compilations of the metabolism in the cases of cardiac disease at the Mayo Clinic, the first includes those studied between March, 1917, and January, 1922, and the second the cases studied during 1922. These results have been combined, and are presented in Table 1 for 849 cases in which are included for comparison the borderline groups, such as essential hypertension, cardiac neurosis and renal disorders. In the tabulation of these cases no consideration was given to the severity of the disease, they were grouped merely according to the main clinical diagnosis.

From these reports it seems unlikely that cardiac disease itself alters the basal or standard metabolism. However, the question is of sufficient importance to justify a more extended analysis of our available data, and to determine if possible the probable cause of the increased metabolism in the few cases in which such is found. For this purpose the clinical, electrocardiographic, and metabolic data have been tabulated and studied in 217 cases of organic heart disease, as the data are very voluminous, and as most of the findings show no correlation with the level of the basal metabolic rate, we shall limit ourselves to a presentation of a summarized statement of the pertinent findings for each general group, a detailed classification was not thought justified.

#### HYPERTENSIVE CARDIAC DISEASE

Twenty-eight cases of hypertensive cardiac disease were observed. The average degree of cardiac decompensation was 2+, on a scale of 0 to 4.

In fourteen of the twenty-eight cases there was decompensation with dyspnea at complete rest and some degree of edema. Three of these cases had normal basal metabolic rates on the

TABLE I

## BASAL METALLIC RATES IN CASES OF CARDIAC DISEASE (Boothby and Sandford)

Percentage range

Cure <sup>a</sup>	Below -20		-20 to -16		-15 to -11		-10 to +10		+11 to +15		+16 to +20		Above +20		-15 to +15	
	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent	Per cent
Essential hypertension 1917 to 1921 Inclusive	110				0.6	73.0	15.8	7.2	3.4							89.4
1922	93				3.0	2.0	66.0	11.0	8.0							79.0
Cardiac neuritis 1917 to 1921 Inclusive	99				1.0	2.0	83.9	10.1	1.0							96.0
1922	22						73.0	23.0	4.0							96.0
Heart block 1917 to 1921 Inclusive	11							80.0	10.0							90.0
1922																
Endocarditis 1917 to 1921 Inclusive	56					1.8	80.4	5.4	1.8							87.6
1922	48					2.0	2.0	65.0	21.0	1.0						88.0
Mycocarditis 1917 to 1921 Inclusive	55					1.8	3.6	81.9	10.9							96.4
1922	10					2.0	2.0	53.0	20.0	13.0						75.0
Pericarditis 1917 to 1921 Inclusive	4								100.0							100.0
1922	5								80.0							80.0
Congenital heart disease 1917 to 1921 Inclusive	5								80.0	20.0						100.0
1922																
Renal disorders <sup>a</sup> 1917 to 1921 Inclusive	127				4.0	1.6	3.2	72.4	12.6	4.0						88.2
1922	80				2.0	2.0	14.0	69.0	4.0	1.0						87.0
Miscellaneous cardiac disorders 1917 to 1921 Inclusive																
1922	33								6.0	67.0	15.0	6.0				88.0
Total																88.0

first determination ( $-8$ ,  $0$ ,  $+7$  per cent). In two cases the initial basal metabolic rate was elevated, but decreased to normal with repetition ( $+14$  to  $+7$  per cent) ( $+19$  to  $+5$  per cent). In a third case there was evidence that decompensation played a rôle in the elevated metabolism, at the time of the first metabolism the patient was orthopneic, and, on digitalis rapidly improved with a gradual decrease in the basal metabolic rate which on four successive days was  $+44$ ,  $+21$ ,  $+17$  and  $+10$  per cent. Decompensation was, however, not the only factor involved in the elevation of the metabolism, because after this improved, the metabolism was still irregularly high as shown the next week on five successive days ( $+18$ ,  $+12$ ,  $+10$ ,  $+15$ ,  $+9$  per cent). Four cases with only two or more determinations showed reductions in the basal metabolic rate, but they did not attain the normal range ( $+27$ ,  $+14$ ,  $+13$ ,  $+11$  per cent), ( $+23$ ,  $+17$ ,  $+18$  per cent), ( $+23$ ,  $+18$ ,  $+13$  per cent) and ( $+12$  to  $+11$  per cent). The presence of decompensation did not in these four cases appear, however, to be the dominating or only factor concerned in the elevation of the metabolism. In four cases in which only a single determination was made a slight elevation of metabolism was found, varying between  $+14$  and  $+20$  per cent.

In ten cases there was a moderate degree of dyspnea on exertion, but no edema. The initial basal metabolic rate was normal in seven of these (ranging from  $-6$  to  $+8$  per cent). In one case the initial basal metabolic rate was elevated ( $+13$  per cent), but returned to normal ( $+7$  per cent) on repetition. In another case, although the first determination was  $+26$ , it decreased to  $+19$  per cent in spite of the simultaneous administration of thyroid extract for obesity, confirming the interpretation that the first determination was not a true basal. In one case in which only one basal metabolic rate was determined, the reading was elevated ( $+15$  per cent).

In four cases there was only slight dyspnea on exertion and of these, three had initial basal metabolic rate determinations that were normal ( $+4$ ,  $0$  and  $+1$  per cent), and one a rate of  $+11$  per cent.

## ARTERIOSCLEROTIC CARDIAC DISEASE

In twenty-nine cases of arteriosclerotic cardiac disease, the average degree of decompensation was 2+. In twenty-four of these there was dyspnea at complete rest, associated with edema, and the initial basal metabolic rates were within the limits of normality. In one case, the first determination was elevated (+19 per cent), while the second determination was normal (+3 per cent). In two cases the initial readings were elevated and did not attain normal with repetition, although these cases were not persistently re-examined (+23 and +23 per cent), (+14, +29, and +18 per cent). In one case, the first and only basal metabolic rate was elevated (+15 per cent).

In four cases in which the dyspnea was only moderate on exertion, the basal metabolic rates at the first examination were normal in two, and in two the readings were slightly elevated (+14 and +11 per cent), no subsequent readings were obtained. In one case in which the dyspnea was slight on exertion, the rate was +11 per cent. The cases of arteriosclerotic disease, therefore, showed no correlation between cardiac decompensation, as such, and an elevated metabolism.

## CHRONIC MYOCARDITIS

There were thirty-nine cases of chronic myocarditis, and the average degree of decompensation was 2+. Dyspnea at complete rest, with edema, occurred in twenty-two cases. In sixteen cases, the initial basal metabolic rate was normal, while in two cases the primary readings were elevated, but became normal on repetition (+29 per cent, and four days later, +9 per cent), and (+18, on repetition +3 per cent). In another case both readings were elevated (+28 and +28 per cent). In three cases in which only one rate was obtained, it was elevated (+15, +14 and +11 per cent).

In ten cases the dyspnea was only moderate on exertion, and in all instances the initial basal metabolic rate was normal (-6 to +6 per cent). In seven cases presenting only slight dyspnea, the first basal metabolic rates in six instances were normal (0 to ±10 per cent). In one case in which only two

readings were taken, the rates were +18 and +14 per cent. There was, therefore, no consistent correlation between decompensation and elevation of metabolism.

#### MYOCARDIAL DEGENERATION ASSOCIATED WITH OBESITY

Only four cases are recorded in this group, and the average degree of decompensation was 2. In three cases there was dyspnea at complete rest, and edema. In one case the initial reading was normal, in one case it was slightly elevated fluctuating on four determinations between +21 and +12 per cent (weight 171 to 160 kg.). In two other cases a single observation indicated that the basal metabolic rate was slightly elevated (+14 per cent).

#### CHRONIC MITRAL ENDOCARDITIS

In ninety-one cases of chronic mitral endocarditis there were stenotic lesions in 45 per cent. The average degree of decompensation in this group (2) was less than that of the foregoing groups. In thirty cases there was edema, and dyspnea at complete rest. In twenty of these cases the initial basal metabolic rate was normal (-8 to +8 per cent). In four cases the initial rate was elevated, but returned to normal on repetition (+17 to +9 per cent), (+18 to +6 per cent), (+13 to +7 per cent), and (+16 to +2 per cent). The initial elevation of the basal metabolic rate recorded in five cases did not attain the limits of normality with repetition (+11, +47, +40, +31, +38, +35, +35 per cent), (+45, +46, +32, +10 per cent), (+12 to +15 per cent), (+15 to +14 per cent), and (+19 to +13 per cent). In the first of these cases the patient was running an irregular temperature which might account entirely for the increased metabolism. In the second, the patient had multiple small adenomas of the thyroid, and was probably hyperthyroid, and therefore does not belong in this report except to illustrate that a patient with severe organic heart lesions of infectious origin may also have the secondary effects of over-work from hyperthyroidism, the aggravation of the cardiac condition by the hyperthyroidism is often entirely overlooked.

In one case in which only one determination was made, the reading was elevated (+32 per cent)

In twenty-five cases in which only a moderate degree of dyspnea occurred on effort, the first basal metabolic rate was normal in fifteen instances (-10 to +8 per cent) In seven cases in which the initial rate was elevated, subsequent determinations revealed normal values (+20 to +2 per cent), (+21 to +9 per cent), (+15 to +10 per cent), (+21 to +9 per cent), (+21 to +7 per cent), (+18 to +3 per cent), and (+13 to +6 per cent) In four cases in which only one reading was obtained, the rates were found to be elevated (+24, +17, +11, and +16 per cent)

In thirty-seven cases the dyspnea was only slight on exertion In this group the initial basal metabolic rate was normal (-10 to +8 per cent) in thirty cases In two cases in which the first rate was elevated, subsequent determinations revealed normal values (+24, +8, -1, +15 per cent), and (+54, +55, +14, +7, +10, +3, +12, +14, +3 per cent) The second of these cases is instructive from the practical standpoint, as it illustrates the difficulty occasionally met with in obtaining complete cooperation on the part of the patient, fluctuations like these without material change in the patient's condition merely mean that basal or standard conditions were not obtained In one case, repeated rates failed to attain normal limits (+17 to +19 per cent) The single rates taken in three cases were elevated (+12, +12, and +11 per cent)

#### CHRONIC ENDOCARDITIS WITH AORTIC REGURGITATION (NON-SYPHILITIC)

In eleven cases of chronic endocarditis with aortic regurgitation, the average degree of decompensation (3) was higher than in any of the other groups

In seven cases the dyspnea was associated with edema at complete rest The initial basal metabolic rate in two cases was normal (-8 and +1 per cent), and in one case the first rates were elevated (+19, +22 per cent), but a week later became normal (+1 and +7 per cent), as the cardiac decompensa-

tion improved. In another case the first two determinations were distinctly elevated, but the last two were nearly normal (+24, +18, +12, +12 per cent). In three cases in which only one rate was taken, the readings were elevated (+13, +11 and +27 per cent).

In four cases there was only moderate dyspnea on exertion. In two of these, the initial basal metabolic rates were normal (+5 and +3 per cent), in another, the first rate was elevated (+14 per cent), and the subsequent rates were normal (+7, +3 per cent), while in the last case both recorded determinations were elevated (+29 and +25 per cent).

#### CHRONIC ADHERENT PERICARDITIS

In seven cases of chronic adherent pericarditis, the average degree of decompensation was 3. In six of these cases there was dyspnea and edema at complete rest, and in five the first basal metabolic rates were normal (-7 to +10 per cent). In one case the first rate was elevated (+21 per cent), but the second reading was normal (+7 per cent). In only one case was there moderate dyspnea on exertion, and the initial basal metabolic rate was normal.

#### CONGENITAL HEART DISEASE

Seven cases of congenital heart disease were studied. The average degree of decompensation was 2. In two cases there was dyspnea and edema at complete rest, the initial basal metabolic rate of one was normal (0 per cent), while the only recorded reading for the other was elevated (+15 per cent).

In four cases there was moderate dyspnea on exertion and the first rate in all instances was normal (0 to +9 per cent).

In one case there was only slight dyspnea on exertion and the initial basal metabolic rate was normal (-6 per cent).

#### CARDIAC NEUROSIS

One hundred cases of cardiac neurosis were studied. In seventy-six cases, the first basal metabolic rate was normal, in twelve the initial rate was elevated but the subsequent rates

were normal. In three cases the recorded rates were all elevated (+17 and +12 per cent), (+19 and +23 per cent), and (+23 and +14 per cent). In nine cases in which only one reading was taken, the rates were elevated (+11 to +29 per cent).

#### DISCUSSION

In the routine determinations of the basal metabolic rate in patients with cardiac disease, the level of the metabolism is found to be slightly elevated above the DuBois standards more frequently than in strictly normal subjects.

This elevation is independent of electrocardiographic findings, and of the type, character or degree of the organic heart lesion. Patients, however, who present evidences of marked cardiac decompensation in the form of dyspnea or orthopnea occasionally have a definite increase in metabolism; in such cases the metabolism usually decreases as cardiac efficiency improves. However, the relative infrequency and irregularity of the increase in metabolism, with or without cyanosis, is against the assumption that the usual cause is the formation of lactic acid from incomplete oxidation, although in a case of extreme cyanosis this might occasionally play a slight part, as suggested by Lusk. In our cases the most probable causes seem to be based on the two following factors. The first is the actual increase in muscular work required in labored respiration. The second, and apparently a more frequently important cause, is the fact that many patients with cardiac disease have a subjective sensation of distress, with resultant nervousness and fear, from the application of the mask or mouth-piece. They are afraid that their breathing will be interfered with. Consequently, it is often difficult to obtain sufficient cooperation from the patient, to assure complete mental and physical relaxation. Likewise patients who have hypertension with a very high diastolic blood pressure are likely to have an elevation in the metabolism, apparently in most cases because they can less readily relax, although other unknown factors may play a part.

On account of the relative frequency of a slight elevation in the metabolic rate in patients with cardiac disease, due, as a

rule, to the difficulty of establishing standard conditions, it behooves the clinician to exercise great caution in interpreting the clinical significance of slight elevations in the metabolism in patients suffering from decompensated heart disease or essential hyperthyroidism. Repeated observations carried out with the greatest attention to detail are necessary to exclude non basal rates. On the other hand, in many cases of adenomatous goiter with hyperthyroidism, the correct diagnosis may be overlooked. A patient with an adenoma of the thyroid, especially if the tumor is quite small, must be considered as hyperthyroid, and the cardiac condition regarded as entirely or partly secondary thereto, provided the metabolism on repeated observations remains above normal. This point is emphasized here because such cases, except one for illustration, have not been included in the present study.

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## ACUTE CORONARY OBSTRUCTION

FREDRICK A. WILLIUS

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The subject of my clinic today is one of unusual interest, from which important observations have been obtained. This man, aged forty-seven years, was admitted to the Mayo Clinic April 21, 1924. He accompanied his wife who came for operation, and considered himself perfectly well. Twenty-eight years before, an operation had been performed on his right ankle for a condition which was said to be tuberculous. Six years before, he had a mild attack of epidemic influenza. Venereal infection was denied. On the morning of April 21, after eating an unusually heavy breakfast, the patient was suddenly seized with severe retrosternal pain radiating into the left arm. He was brought to the Clinic within half an hour, and a physician administered 1/75 gr. of nitroglycerin under the tongue, without relief. The patient was immediately hospitalized on the cardiologic service, and  $\frac{1}{4}$  gr. of morphin sulphate was administered hypodermically.

Examination revealed a small man, appearing older than his years. His facies were those of extreme suffering, and he had a pasty pallor. The cardiac dulness extended 3 cm. to the right, and 9 cm. to the left of the median sternal line. A respiratory arrhythmia was present, but the tones were clear, and the rate 75 each minute. There was a moderate degree of peripheral arteriosclerosis. The systolic blood pressure was 130, and the diastolic 90. An electrocardiogram taken fifteen minutes after admission to the hospital (Table 1, Record 1) revealed only a slight sinus arrhythmia and exaggeration of the T wave in Derivations II and III. The pain lasted seven and one-half hours, and was not relieved by four hypodermatic injections of morphin. A diagnosis of coronary thrombosis was made. Roent-

rule, to the difficulty of establishing standard conditions, it behooves the clinician to exercise great caution in interpreting the clinical significance of slight elevations in the metabolism in patients suffering from decompensated heart disease or essential hyperthyroidism. Repeated observations carried out with the greatest attention to detail are necessary to exclude non-basal rates. On the other hand, in many cases of adenomatous goiter with hyperthyroidism, the correct diagnosis may be overlooked. A patient with an adenoma of the thyroid, especially if the tumor is quite small, must be considered as hyperthyroid, and the cardiac condition regarded as entirely or partly secondary thereto, provided the metabolism on repeated observations remains above normal. This point is emphasized here because such cases, except one for illustration, have not been included in the present study.

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## ACUTE CORONARY OBSTRUCTION

FREDRICK A WILLIUS

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The subject of my clinic today is one of unusual interest, from which important observations have been obtained. This man, aged forty-seven years, was admitted to the Mayo Clinic April 21, 1924. He accompanied his wife who came for operation, and considered himself perfectly well. Twenty-eight years before, an operation had been performed on his right ankle for a condition which was said to be tuberculous. Six years before, he had a mild attack of epidemic influenza. Venereal infection was denied. On the morning of April 21, after eating an unusually heavy breakfast, the patient was suddenly seized with severe retrosternal pain radiating into the left arm. He was brought to the Clinic within half an hour, and a physician administered 1/75 gr of nitroglycerin under the tongue, without relief. The patient was immediately hospitalized on the cardiologic service, and  $\frac{1}{4}$  gr of morphin sulphate was administered hypodermically.

Examination revealed a small man, appearing older than his years. His facies were those of extreme suffering, and he had a pasty pallor. The cardiac dulness extended 3 cm to the right, and 9 cm to the left of the median sternal line. A respiratory arrhythmia was present, but the tones were clear, and the rate 75 each minute. There was a moderate degree of peripheral arteriosclerosis. The systolic blood pressure was 130, and the diastolic 90. An electrocardiogram taken fifteen minutes after admission to the hospital (Table 1, Record 1) revealed only a slight sinus arrhythmia and exaggeration of the T wave in Derivations II and III. The pain lasted seven and one-half hours, and was not relieved by four hypodermatic injections of morphin. A diagnosis of coronary thrombosis was made. Roent-

## SUMMARY OF ELECTROCARDIOGRAMS

Record	Day of illness	Heart rate	Electrocardiographic findings.	Re-marks
1	First	75	Sinus arrhythmia exaggerated T wave in Derivations II and III	Taken during attack
2	Second	95	Alternating nodal premature contractions	No pain
3	Third	100	Sinus tachycardia negative T wave in Derivation I and QRS complexes in Derivations II and III suggesting right bundle branch block	No pain
4	Fourth	97	Sinus tachycardia negative T wave in Derivations II and III the T wave in Derivation I becoming positive Bundle branch block effect absent	Patient comfortable.
5	Fifth	103	Sinus tachycardia same as in Record 4 except that slight preponderance of the left ventricle is present	No change
6	Sixth	100	Sinus tachycardia, negative T wave in Derivations II and III the T wave in Derivation I becoming positive Bundle branch block effect absent Slight preponderance of the left ventricle present	No change
7	Eighth	92	Sinus tachycardia negative T wave in Derivation I T wave positive in Derivations II and III slight left ventricular preponderance	No change
8	Ninth	90	Sinus tachycardia, negative T wave in Derivation I T wave positive in Derivations II and III, slight left ventricular preponderance	No change
9	Tenth	95	Sinus tachycardia negative T wave in Derivation I T wave positive in Derivations II and III slight left ventricular preponderance	No change
10	Eleventh	92	Sinus tachycardia negative T wave in Derivation I the amplitude increasing T wave positive in Derivations II and III, and the preponderance of the left ventricle more marked	No change
11	Twelfth	103	Sinus tachycardia negative T wave in Derivation I the amplitude increasing T wave positive in Derivations II and III, and the preponderance of the left ventricle more marked	No change
12	Thirteenth	100	Occasional ventricular premature contractions otherwise same as in Record 11	Up in chair fifteen minutes
13	Fifteenth	100	Sinus tachycardia negative T wave in Derivation I left ventricular preponderance	Up in chair one-half hour
14	Seventeenth	100	Sinus tachycardia negative T wave in Derivation I left ventricular preponderance	Up in chair one hour
15	Nineteenth	90	Sinus tachycardia, negative T wave in Derivation I left ventricular preponderance	Up in chair two hours
16	Twenty-second	94	Sinus tachycardia negative T wave in Derivation I left ventricular preponderance	Up in chair three hours
17	Twenty-fourth	100	Sinus tachycardia negative T wave in Derivation I left ventricular preponderance	Up in chair four hours
18	Twenty-sixth	103	Sinus tachycardia negative T wave in Derivation I left ventricular preponderance	Up in chair five hours
19	Twenty-eighth	96	Frequent ventricular premature contractions otherwise same as in Record 18	Up in chair six hours
20	Twenty-ninth	10	Very frequent ventricular premature contractions otherwise same as in Record 18	Up in chair seven hours
21	Thirty-second	95	Occasional ventricular premature contractions sinus tachycardia negative T wave in Derivation I left ventricular preponderance The amplitude of T wave has changed from -2.75 to -3.5 m	Up in chair eight hours

genologic studies of the chest made the same day revealed a normal cardia. The leukocyte count was 6,800, and the blood Wassermann reaction was negative. A faint trace of albumin was found in the urine. The maximal temperature for the day was 100° F.

Treatment consisted of complete rest in bed and a restricted low protein diet. No medication was given after the first day, when nitroglycerin and morphin sulphate were administered.

**Course**—There were no changes in the objective findings the day after the treatment was instituted, there had been no repetition of pain, but the patient was extremely anxious and apprehensive. The development of a pericardial rub, which we expected would appear as the result of a localized pericarditis over the infarcted area, was carefully sought, but was not detectable during the whole period of observation. On the second day the leukocyte count had risen to 12,000. The maximal temperature for this day was 101° F. Alternating nodal premature contractions were present in the electrocardiogram. On the third day the physical findings were unaltered, and the patient was comfortable. The maximal temperature for the day was 99.6° F., and the leukocyte count was 13,900. The electrocardiogram revealed marked changes, in no way resembling those of the previous days. The T wave was negative in Derivative I, and the QRS complexes in Derivatives II and III were those of right bundle branch block. On the fourth day no change was noted in the physical findings, except that the heart rate was constantly over 90. The temperature was normal. The electrocardiogram on this day was again markedly different. The T wave, which on the preceding day had been negative in Derivation I, became positive, and the T waves in Derivations II and III became markedly negative. The findings of right bundle branch block disappeared. This form of electrocardiogram persisted for three days, when the T wave became negative in Derivation I and positive in Derivations II and III, and preponderance of the left ventricle became apparent. These graphic findings remained constant throughout the period of observation except for a few minor changes.

The heart gradually dilated, so that at the time of the patient's dismissal, on the thirty-second day after the attack, the cardiac dulness extended 4 cm to the right and 12 cm to the left of the mid-sternal line. The tones were rapid and muffled, but no murmurs were audible. Very slight effort, such as arising from a chair, caused dyspnea. Therefore, the patient's activities were rigidly restricted, and he was advised to continue the restrictions indefinitely. Intermittent digitalization was suggested to his home physician.

#### DISCUSSION OF ELECTROCARDIOGRAMS

This is one of the few cases of acute coronary obstruction on record that has been carefully studied with the electrocardiograph. The electrocardiograms are too numerous to reproduce here, but some of them have been published elsewhere.\* Correlation of electrocardiographic and physical findings permit interesting speculations as to the location of the myocardial infarct. The fact that, on the day after the occlusion, alternating nodal premature contractions were present, and that on the next day a block of the right bundle branch occurred, suggests a disturbance near the auriculoventricular node and right bundle branch. The absence of a pericardial friction suggests that the infarct may have occurred on the posterior portion of the heart. If so, the area of involvement was possibly on the posterior aspect of the upper portion of the right ventricle. Since the accident was not fatal, the artery occluded was probably a small branch.

#### DIAGNOSIS

The elicitation of a careful history is of primary importance in the diagnosis of coronary thrombosis. The case under discussion is unusual in that there was a total absence of cardiac symptoms prior to the acute obstruction. There is frequently a history of preceding anginal attacks, dyspnea on effort, or attacks of paroxysmal dyspnea. The most striking symptom-

\* Willius, F. A., and Barnes, A. R. Myocardial infarction. An electrocardiographic study. A report of nine cases from the Mayo Clinic, and a review of twenty-four published cases. *Jour. Lab. and Clin. Med.*, 1925.

atic feature is the persistence of pain, usually from one to seven or eight hours, but in one case that came under my observation, twenty-four hours. Prolongation of an anginal attack should always direct attention to the probability of acute coronary obstruction. The origin and distribution of pain are not always typical. The pain may be retrosternal and radiate into the left arm or both arms; it may be in the epigastrium without radiation, or it may arise in other regions. Death may be instantaneous, or life may be prolonged for a few hours or days, and occasionally recovery occurs with varying degrees of cardiac incapacity.

During attacks patients are likely to have a pasty, almost ashen pallor. Their skin is usually cold and clammy; their features are drawn with suffering and they have an anxious look, due to the invariable apprehension. Dyspnea commonly accompanies the pain, is often constant, at times paroxysmal, and in the later stages may be of the Cheyne-Stokes type. Nausea and vomiting may occur, and tend to mislead the clinician, particularly when the pain is located in the abdomen. Occasionally patients with myocardial infarction will suddenly become hemiplegic, and die with all evidences of a cerebral accident, particularly if the infarct is near the apex of the left ventricle, so that a mural thrombus develops in that chamber. In such cases, death results from cerebral embolism from detachment of a portion of the mural thrombus.

Examination invariably reveals enlargement of the heart, usually to the left of the mid-sternal line. The heart tones are usually distant and rapid, and occasionally barely audible. Systolic apical murmurs are not infrequent, particularly if there is dilatation of the left ventricle. Aortic systolic murmurs likewise occur, as a distinct degree of aortic sclerosis commonly accompanies sclerosis of the coronary arteries.

In case of death soon after the accident, the infarcted area will be clearly demarcated and confined to the region supplied by the obstructed artery. At times the infarct is hemorrhagic and stands out in clear relief from the surrounding myocardium. The myocardium is often the seat of a patchy, or a rather dif-

fuse fibrotic process. Associated with a recent infarct there is at times evidence of an old, slowly developing or chronic infarct, manifested as a thinned out, cicatricial area, usually the result of gradual obliterating atherosclerosis.

Histologic study of a recent infarct reveals acute necrosis of the muscle bundles with segmentation and fragmentation of fibers. The muscle is often granular in appearance, and an infiltration of polymorphonuclear leukocytes usually occurs. An area of localized pericarditis overlying the infarct may be present, but rarely is the amount of pericardial fluid appreciably increased.

#### TREATMENT

There is little to be done for this condition except to alleviate the patient's suffering as much as possible. The administration of morphin is probably the most effective for this purpose although in the case cited, little relief was obtained by its use. In my experience the nitrites have given little or no benefit. The application of leeches to the precordium has been recommended.

If the patient survives the severe cardiac insult, and there are manifestations of myocardial failure, the use of digitalis is indicated. The dosage and method of administration must always be determined by the circumstances in the individual case. The presence of a pericardial friction rub due to localized pericarditis over the infarcted area is strong confirmatory evidence, but its absence is not significant. The rub is usually heard over the lower sternum, or just to the left of the sternum.

Premature contractions are frequently present, but their occurrence is not diagnostic. Moist râles at the base of both lungs is a common finding. Fever, ranging from 99.6° to 103° and 104° F is quite the rule, appearing often a few hours after the accident. There is usually a definite leukocytosis, the count varying from 11,000 to 25,000.

The electrocardiograph is helpful in substantiating acute coronary obstruction. The most constant findings in thirty-one reported cases were changes in the T wave consisting of negative, diphasic and iso-electric deflections in Derivation I, in

- Derivations I and II, in Derivations II and III, and in Derivations I, II, and III In four cases, fusion of the R and T waves occurred, and in five instances aberration of the QRS complexes in all derivations were recorded

#### PATHOLOGY

Pathologic examination of the hearts of patients dying as the result of coronary thrombosis invariably reveals extensive arteriosclerosis of the coronary arteries. The aorta likewise is the seat of disease, consisting of sclerosis, atheroma, and ulceration. As a rule, a single arterial branch will be occluded by a thrombus, although occasionally more than one branch will be obstructed. The anterior descending branch of the left coronary artery is the one most often occluded.



## THREE CASES OF VASCULAR DISEASES AFFECTING THE FEET

(Thrombo-angitis Obliterans, Raynaud's Disease, and Erythromelalgia)

GEORGE E. BROWN

Three cases illustrating different types of vascular disturbance of the feet are presented. Considerable confusion exists in differentiating such cases. An accurate clinical diagnosis is not only of importance from the academic standpoint, but from the standpoint of rational treatment. The problem in diagnosis is to determine whether the vascular disturbance is an obliterative or vasomotor lesion, and then to determine the type of obliterative or vasomotor lesion.

The obliterative or occlusive arterial lesions of the extremities comprise two main types—arteriosclerosis, and thrombo-angitis obliterans, or Buerger's disease. The more rare types of occlusive disease, such as arteritis of rheumatic or syphilitic origin, need only be mentioned. The embolic or thrombotic lesion involving the extremities usually presents a clinical picture which need not be confused with the more chronic types of arterial lesions.

The diagnostic difficulties in the individual case are greatly simplified by the determination of whether the basic disturbance is obliterative or vasomotor. This decision rests primarily on the presence or absence of arterial pulsation in the vessels proximal to the lesion. Accuracy in determining this point is the sine qua non of vascular diagnosis. The femoral, popliteal, posterior tibial and dorsalis pedis vessels should be carefully examined for the presence of pulsations. Considerable practice is necessary in doubtful cases in order to decide this point.

definitely. A thorough knowledge of the course of these vessels and of the types of normal pulsation is necessary before accurate conclusions can be drawn. The following landmarks will facilitate the course of these vessels.

The surface marking of the dorsalis pedis is fairly well defined by drawing a line on the dorsum of the foot from the center of the space between the internal and external malleoli to the

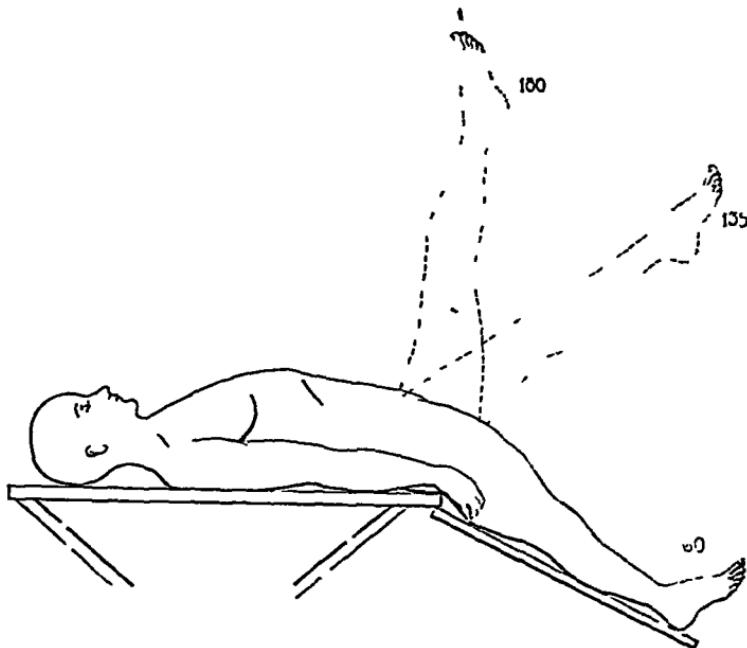


Fig. 191.—The technic for performing the circulatory efficiency test. In the normal person the color of the foot is maintained at 180 degrees, with slight reddening at 60 degrees or less. In the presence of an arterial obstruction marked pallor appears at 180 degrees, and reactionary hyperemia in the pendent position. (From Buerger.)

division of the first and second toes. The posterior tibial artery can be easily palpated in the space between the heel and the internal malleolus. The popliteal artery is best examined with the patient lying full length, face down, knees fully flexed, thus relaxing the surrounding muscles. By inserting the examining finger deeply internally and medially to the biceps tendon, pulsation is easily felt. Occasionally considerable pressure is

necessary to accomplish this. If patients have feeble or intermittent pulsations, great care must be taken to differentiate subjective pulsatory sensations that are felt by the examiner's fingers, particularly in the dorsalis pedis, where extremely light palpation is necessary. The Pachon oscillometer is often very useful in determining the existence, as well as an index, of

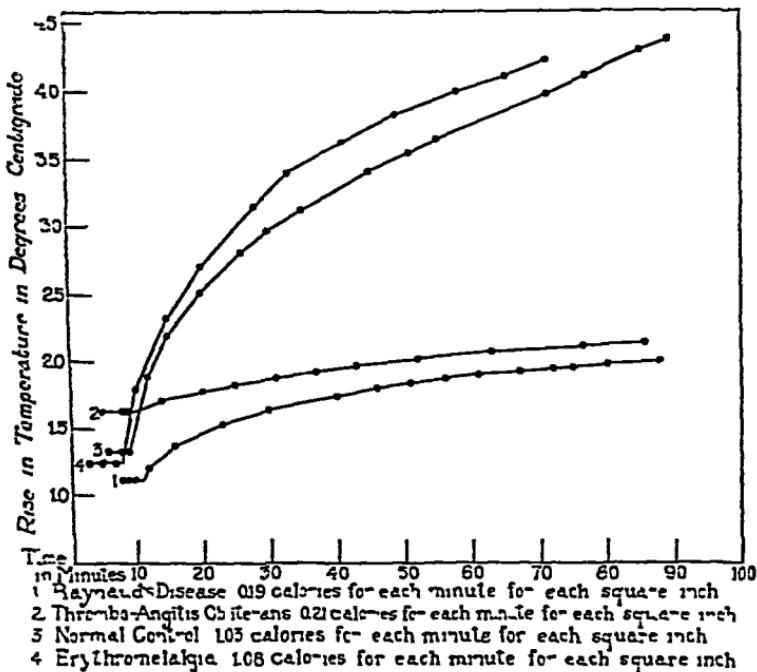


Fig. 192.—Curves showing the heat production of the foot in normal persons, and in those with different types of vascular disturbances, as determined by the Stewart calorimeter. The final result is given in calories for each minute for each square inch of surface area. The normal heat production of the feet varies from 1 to 2 calories each minute for each square inch.

the degree of pulsation in doubtful cases. If arterial pulsation is absent, it is assumed that the obliterative type of lesion is present. There is a secondary group of secondary signs and symptoms which, if found, will substantiate this diagnosis. These are (1) color of the limb, such as pallor, cyanosis or hyperemia which is modified by change of position (Fig. 191), or the cir-

culatory efficiency test,\* (2) decreased temperature or coldness of the affected leg as revealed by touch and calorimetric studies, (3) trophic disturbances such as thickened nails, trophic ulcers, localized calluses, and excessive cornification, (4) gangrene, and (5)  $x$ -ray evidence of localized arteriosclerosis of the vessels of the leg. The symptoms of the organic occlusive lesions are of two major types: pain related to tissue anoxemia or intermittent claudication, and pain related to superimposed infection. These two types of pain can be easily separated, and they represent an entirely different etiologic basis. The signs and symptoms are fairly representative of both arteriosclerosis and thrombo-angiitis obliterans. The differential diagnosis of these two conditions rests largely on other collateral evidence. The data that would be necessary to define the cases as those of localized arteriosclerosis are (1) the more advanced age of the patient, (2) the  $x$ -ray signs of arteriosclerosis and demonstrable arteriosclerosis in other vascular areas, (3) the shorter clinical course, as compared with thrombo-angiitis obliterans, (4) the greater incidence of associated diabetes, (5) the greater incidence of moist gangrene, (6) the absence of racial factors, and (7) the absence of preceding phlebitis, which is so common in cases of thrombo-angiitis obliterans.

In certain cases in which clinical diagnosis could not be made with accuracy, biopsies of superficial veins or arterial twigs have been made, and thus in many instances an absolute diagnosis was obtained.

The vasomotor group is large, and includes two distinct clinical types, Raynaud's disease, or symmetrical gangrene, and erythromelalgia.

Closely related to Raynaud's disease is a large group of clinical conditions, including acrocyanosis, peripheral syncope or dead fingers, and a condition in which there are three distinct color phases, with or without slight trophic disturbances, the latter is probably an incomplete or mild form of Raynaud's

\* Elevation of the legs to 180° produces a marked pallor in the presence of arterial occlusion, lowering of the leg to 65° or zero, following a variable latency period, induces a reactionary hyperemia (Fig. 192).

disease. These borderline cases may represent varying degrees of the same underlying condition as noted by Muller. However, it is probably wise, as Buerger has pointed out, to maintain as a clinical entity the cases in which there are attacks of pain, color changes and trophic disturbances, such as gangrene, or

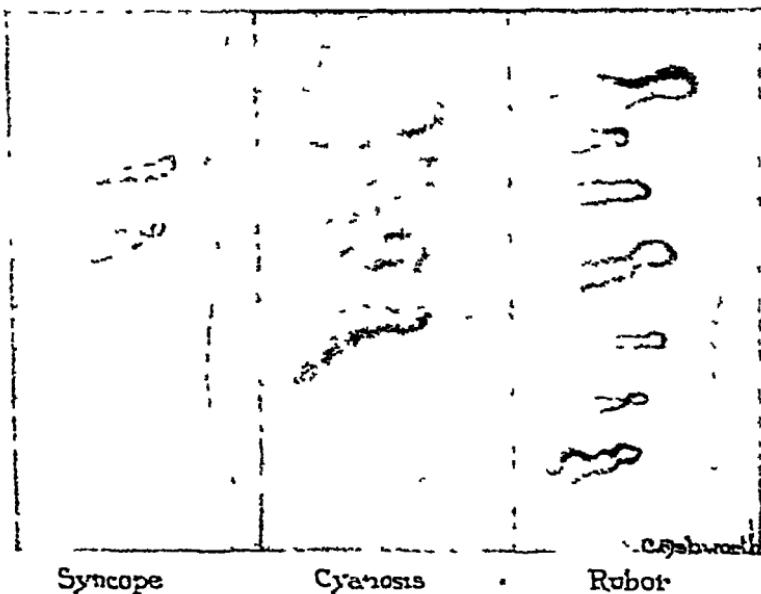


Fig. 193.—Appearances of the capillaries of the skin in the different color stages in Raynaud's disease. These represent the same groups of capillaries in the three different color phases. In the white-blue stage the capillaries are contracted, imperfectly filled, with no movement of capillary blood. In the blue phase, the loops are dilated, some blood entering from the arterioles and venules, with complete stasis in most loops. The broken appearance of the stream probably is an agglutination phenomenon. In the red stage there is resumption of capillary flow, the loops still being dilated.

true Raynaud's disease. In Raynaud's disease and allied vasomotor states (Fig. 193), the disturbances in capillary flow (stasis, plasma gaps, and alternating active and inert flow) and abnormal cold reactions are present in the mild and severe cases of vasoneuroses, the difference being only one of degree. The diminished capillary tone which is recognized as dilatation

is constantly present in these cases. This is additional evidence which makes us believe that the difference between the mild vasomotor disturbances and Raynaud's disease is one of degree only, that this type of vasomotor disturbance has a constitutional basis, and is related to a disturbance of the vegetative nervous system and psychic centers.

The usual signs and symptoms in cases of vasoneurosis, or the Raynaud group, are as follows: (1) pulsations in all the peripheral arteries, (2) abnormal color reactions, rubor, local syncope, cyanosis, usually initiated by cold, (3) pain of varying degrees, or paresthesia, associated with the color changes, (4) the presence of trophic disturbances varying from small dried punctate ulcers to a well-defined dry gangrene, and (5) evidences of a general constitutional inferiority, comprising the asthenic types with lowered blood pressure, cold extremities and poor vasomotor reactions.

An exact classification of erythromelalgia has not been made. Pathologic studies are lacking, but the clinical investigations have shown conclusively that this is the non-obliterative type of vascular disorder, and hence it is classified as a vasomotor disturbance. Wer Mitchell described the condition in 1878, noting paroxysmal attacks of pain, redness and swelling of the feet. Motor, secretory and trophic disturbances occur occasionally, and hyperesthesia more often. Points essential to establishing the diagnosis are (1) redness of the feet, usually intensively aggravated by the pendant position and heat, and relieved by elevation, and by cold, (2) pain, usually of two types, intense burning or deep aching, often referred to the ball of the foot or the heel, (3) paresthesia, usually confined to the hyperemic areas, (4) redness, usually bright, or with an intense blush tinge, and associated with increased arterial pulsation and dilatation and distention of the peripheral veins, (5) normal or increased temperature of the skin, as determined by touch and calorimetric studies, (6) swelling, undoubtedly due to increased blood supply since elevation of the limb is accompanied by diminished swelling, (7) trophic disturbances, such as blebs, atrophy of the skin, and dystrophic

disturbances of the skin and nails (if associated with gangrene, the diagnosis of erythromelalgia would be improbable), and (8) secretory disturbances revealed by excessive sweating, which is common during attacks

**Case 1 Thrombo-angitis obliterans, or Buerger's disease**—A man, aged forty-six years, was admitted to the Clinic June 8, 1923. He had used tobacco excessively, and had had chilblains on both feet until eight years before examination. Five years before, the superficial veins of the legs became swollen, tender and red. This disappeared after several weeks. One year later claudication was noted in both legs, more marked in the left. Following the wearing of arch supports, several superficial abscesses developed in both feet, but cleared up in three months. At about the same time tingling developed in the right great toe, which was white and cold. The sensation of cold was relieved by massage. One month later an infection of this toe developed, and did not heal for nine months. During the years 1921 and 1922, cramps in the legs were very troublesome when attempts were made to walk. Six months before examination the nail of the left great toe became greatly thickened, and was removed by a local physician, infection developed and persisted.

Examination revealed rubor of the left foot in the pendant position, the veins were prominent. There was an ulcerated area on the first toe. The foot felt cold to touch. The pendant position produced moderate rubor and some edema in the right foot. Pallor was evident in both feet when elevated to 180°. No pulsations were detected in the dorsalis pedis, posterior tibial, and popliteal vessels of either foot. X-ray examination of the left foot disclosed phalangeal destruction of the great toe. Medical treatment, consisting of rest, hot lights, and sedatives, for a period of ten days, failed to give relief.

Sympathectomy was performed June 19, 1923, on the left femoral artery. Exposure of this did not reveal pulsation, the vessel was about one-third normal size. There was marked periarteritis. The penarterial tissue was injected with 15 mm of 95 per cent alcohol. Following operation, the patient was relieved from pain for a period of three days. No demonstrable change in color, temperature of the skin, or pulsation of vessel was noted. August 1, the first and second toes of the left foot were amputated. The healing was slow, and relief not complete. September 18, the left thigh was amputated in the lower third. The blood vessels were small and greatly thickened. The blood supply was definitely impaired, as shown by the removal of the tourniquet. The patient recovered uneventfully, and returned home. Six months later, the right foot showed evidence of adequate circulation for a restricted life. There was erythromelgia in the pendant position. The skin of the foot was healthy, and there was no pain. Sections of the popliteal, and tibial artery, and the dorsalis pedis, showed the end stage picture of thrombo-angitis obliterans. The thrombus was organized with some canalization. No acute lesions were found.

*Comment*—This case represents an example of the obliterative type of vascular lesion, as was evidenced by the absence of pulsation in the peripheral vessels of the feet, avascular appearance of the foot at  $180^{\circ}$ , and the resultant reactionary hyperemia in the pendant position or at  $0^{\circ}$ . The trophic dis-



Fig. 194.—Photomicrograph showing cross-section of artery and vein in case of thrombo-angitis obliterans. The thrombi show complete filling of the vascular lumina, and new blood channels are being formed within the clot as the result of angioblastic activity. Note the periarterial fibrosis, binding artery and vein together.

turbances of the feet, the low temperature of the skin, and claudication pain contributed further evidence to the obliterative basis of the complaint. The differential diagnosis between the two main types of obliterative arterial disease was made on the following clinical evidence: the age of the patient, the

absence of demonstrable arteriosclerosis on x-ray examination of the feet, and the long history (five years). The history of preceding phlebitis made the diagnosis of thrombo-angiitis obliterans fairly conclusive, and this was proved by the pathologic examinations of the vessels in the dissected limb, which revealed the obturating thrombus formation in the end-stage of organization. Canalization had taken place with some degree of arterial function (Fig. 194).

Thrombo-angiitis obliterans is treated both medically and surgically. Unfortunately the majority of the patients, when first seen, have gangrene with superimposed infection, and extremely distressing pain, and hence, surgical intervention or amputation is usually indicated. The patient's morale and the danger of the opiate habit are serious considerations which lead to the decision to amputate. In the absence of gangrene, a fair degree of arterial compensation is often obtained by various measures. Restriction of the patient's activity to a degree commensurate with his vascular handicap, and sometimes long periods of from three to six months of greatly restricted life are beneficial. The exact cause of the disease is unknown, however, it is believed to be of an infectious nature, and an effort should be made to eradicate all foci of infection.\* Increased blood supply is encouraged by prolonged applications of dry heat, electric light baths with low degree heat being given for periods of one to four hours daily. Extreme caution must be exercised to prevent burning, for the skin resistance is already low in these cases. Postural exercises consisting of elevation and lowering of the limb at a rate of one or two times each minute may be given for fifteen-minute periods, two or three times daily. Injections of a 2 per cent solution of sodium citrate are given intravenously, 250 c.c. every second day for a course of forty injections are beneficial. Prophylactic measures to prevent the infecting of feet after the patient is dismissed from observation are important. Many such patients

\*Striking improvement has been observed in two cases following the removal of badly infected tonsils. Conversely, definite flare-ups have been noted in the disease following acute tonsillar infection.

do fairly well until meddlesome measures in the care of feet cause infection and subsequent gangrene

In a series of over forty cases treated in the Mayo Clinic in the last two years, encouraging results have followed persistent medical treatment. Nevertheless, surgical intervention should not be delayed too long if gangrene is present and progressive.

**Case 2** Raynaud's disease.—A man, aged fifty two years, was examined at the Clinic August 9, 1923. Two years before, following exposure to cold, tingling in the middle toe of the right foot was followed by a dull aching pain and permanent cyanosis. The toe became gangrenous and was amputated. Healing was uneventful. A similar cyanotic change, and a trophic ulcer appeared in the first toe, this healed with rest and local heat applications. One year before examination, the first toe of the left foot became cyanotic and painful, and was amputated. Relief followed, but the cyanotic areas persisted, and trophic disturbances appeared on both feet, healing very slowly. Six weeks before examination, a similar course of events occurred in the first and middle fingers of the left hand, with severe pain, which was aggravated by cold damp weather. There was no history of claudication. Double sympathectomy in the femoral arteries had been performed elsewhere sixteen months before. No demonstrable benefit was received.

On examination general arteriosclerosis 2 of the peripheral vessels was noted. Ophthalmoscopic examination revealed retinal vessels irregular in caliber with moderate arteriovenous compression. The heart was enlarged 1 with no murmurs. The systolic blood pressure was 170, the diastolic 100. The hands were cold and the first and third fingers markedly cyanotic. On the tip of the first finger was a small ulcer. The color of the skin was maintained in the hand at an elevation of 180°. Both feet were markedly cyanotic and cold to touch. The circulatory efficiency test revealed a mottled, pinkish cyanotic appearance of the hands and feet, which returned quickly to the previous color at 90° in one minute. There were patchy cyanotic capillary areas in the lower axilla, crest of the ilium, and thighs. The arteries of the leg and arm were palpable with good pulsation. A moderate degree of tortuosity was present in the radial arteries. The oscillometric index was normal in both feet. Many of the capillaries of the skin were thrombosed, the active vessels showed dilatation, stasis and plasma gaps (Fig. 193). The phenolsulphonephthalein return was 35 per cent in two hours. The maximal concentration of urine was 1.021.

Treatment consisted of hot and cold contrast baths, and sodium nitrite, 0.03 gm every hour, for six doses daily. Anterior lobe pituitary extract was given without noticeable improvement, except some relief from pain. The patient returned to the Clinic seven months later. The color and subjective sensation had gradually improved. There was slight dyspnea. Following exposure to extreme cold, a relapse had occurred, but relief had been obtained by use of the hot and cold foot baths.

*Comment*—The history of the development of the symptoms in this case is almost pathognomonic. The permanent cyanosis, followed by gangrene, color changes, and attacks of pain in other acral areas made the diagnosis of Raynaud's disease certain. The examination of the extremities revealed the presence of open arterial paths and pulsations. This places the case in the group of vascular disturbances of the nonobliterative type, thus having a vasomotor basis. The circulatory efficiency test showed incomplete pallor at 180°, which was changed very little at 90 and 0°. There was no reactionary hyperemia. The examination of the capillaries of the skin and of the toe nail-fold revealed thrombosed vessels. In the finger nail-fold were large dilated loops during the red stage, with stasis in many loops and plasma gaps. The latter phenomenon seems dependent on an agglutination process secondary to abnormal capillary permeability and inert capillary flow. The appearance of the capillaries of the skin in various types of vasomotor neurosis, grouped collectively under the name of Raynaud's syndrome, is apparently pathognomonic, and seems to add additional evidence of the close relationship between the mildest cases of acrocyanosis and the full blown cases of Raynaud's disease.

The treatment of Raynaud's disease is unsatisfactory. It is interesting to note the lack of beneficial response following sympathectomy, although as the operation was performed elsewhere, the exact technic is unknown. It would seem on a priori grounds that this type of case would be the most favorable for this type of operation. There is much, however, to be learned regarding the vasomotor nerve paths, and too positive statements regarding the physiologic effects of stripping the adventitial layer of one arterial segment cannot be made. Medical treatment has been directed towards the re-education of the vasomotor response, by the so-called contrast baths. Alternating hot and cold foot plunges are given for fifteen-minute periods three times a day, changing from hot water (105°) to cold water (20°), three or four times each minute. Alternating hot and cold body showers and air baths with increasingly cold environmental temperatures are also advised. In this manner, a

gradual beneficial hardening is instituted. The administration of vasodilating drugs, such as sodium nitrite in a few cases has relieved the pain slightly, but no quantitative changes could be demonstrated by means of the calorimetric studies. The other lines of treatment directed towards increasing the general body tone are high calorie, high protein diets, prolonged rest periods, and removal of injurious psychic factors where possible.

**Case 3. Erythromelalgia**—A man, aged fifty-seven years, was admitted to the Clinic June 11, 1923. The patient's illness dated back twenty-two years, and was apparently related to his work, as he was a painter and stood on ladder rungs many hours a day. He first noted soreness on the balls of his feet on walking. This extended to the ankles and he was obliged to give up his work. The condition had become progressively worse, so that weight of any degree on the feet had become unbearable. The feet had become red gradually, and this was more marked in warm weather and in the pendant position. He walked on his hands and knees, or used crutches. Relief followed elevation of the leg, cold weather, or cold applications. Two types of pain were complained of: a superficial burning sensation on the dorsum of the toes associated with rubor, and a deep-seated, dull aching on the inner aspects of both feet. The former was completely relieved by elevation and cold, the latter, only partially so.

On examination, both feet were intensely red, and the veins markedly distended. The skin was moist and warm. The dorsalis pedis arteries were easily palpated. When the feet were elevated to 180°, they were paler, the veins collapsed, and pulsations were present in all vessels. There were no trophic changes present. Hyperhidrosis was present, more marked when the feet were red. Roentgenograms of the feet did not reveal evidence of arteriosclerosis. The blood flow was normal in both feet. Sympathectomy was performed on the left femoral artery. The adventitial tissue was separated from the muscular coat and removed. Alcohol was injected in the subadventitial layer. The arteries were pulsating and normal in size. No subjective or objective change was noted following operation. The patient was allowed to go home with instructions to return for further observation.

Four months later the patient returned. No improvement had been noted. The examination showed no change in condition. At this time the skin of both legs was injected with 0.5 per cent solution of novocain, in order to produce stocking anesthesia. The feet were then examined in the pendant position. Hyperemia quickly appeared. There was slight pain in the left foot. Relief from the burning sensation persisted for about three hours after this treatment. The deep pain was not affected. As results following the injection were equivocal, further injections were not considered advisable. Much relief was obtained during the summer months by going barefoot in wet grass and sand on a river bank, but in general, the condition has remained stationary.

*Comment*—The cardinal diagnostic features of erythromelalgia, described by Weir Mitchell in 1878, were (1) pain, usually of a burning type varying from mild hyperesthesia to that of extreme torture, (2) aggravation of pain by exercise and heat, (3) amelioration of pain by cold and elevation of the limb, (4) flushing of the extremities, varying from a dull mottled redness to an intense crimson color, and (5) distention of veins and throbbing of the arteries associated with slight swelling of transitory nature.

The preliminary examination in this case showed at once that the condition was not of the obliterative type, but that during the attacks there was an increased blood supply, as revealed by the color, temperature of the skin, and the patient's subjective feelings. This would indicate vasomotor dilatation, producing the opposite condition to that observed in Raynaud's disease. As pointed out by Weir Mitchell, the onset of pain precedes the development of the vasomotor phenomena. It is probable that the vasomotor symptoms in these cases are secondary manifestations of manifold pathologic processes. Minor bone changes have been described by some writers. In one case observed in the Clinic, a mild degree of periostitis was present.

The treatment, in lieu of an etiologic basis, is symptomatic. The stripping of the sympathetic nerves in the adventitial layer of the femoral artery was ineffective in this case. All medical treatment was without avail. The patient's greatest relief was obtained by going barefoot in the summer months, and by the wearing of light hose and ventilated shoes during the winter months. Intragluteal injections of antimony, as suggested by Clarke, were tried. Slight relief was obtained, according to the patient. He was not under observation, so that objective evidence was not obtained. One patient was recently treated for this condition with alternating hot and cold baths, the administration of large doses of salicylate and eradication of a focus of infection in the prostate. Very striking relief was obtained from both the hyperesthesia and the deep-seated, throbbing pain in the heel.

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## POSTARSPHENAMIN JAUNDICE

PAUL A O'LEARY

I shall present the case records of four patients who have been under treatment for syphilis, three of whom have had the misfortune to develop jaundice as a complication. Particular emphasis will be placed on the value of the hepatic functional tests as an aid in diagnosis and treatment of postarsphenamin jaundice, as well as a guide to further antisyphilitic treatment following hepatic complications.

The belief that all cases of postarsphenamin jaundice are the result of the effect of the arsenic on the liver cells has been too readily accepted. Various causes for the development of jaundice following the intravenous use of arsphenamin have been recognized at the Clinic. They are as follows:

- 1 Toxic or infectious hepatitis
- 2 Arsenical hepatitis going on to atrophy
- 3 Syphilitic disease of the liver, (a) Herxheimer effects, (b) syphilitic hepatitis too vigorously treated resulting in a too rapid fibrosis, (c) jaundice of acute syphilis, (d) recurrence of syphilis of the liver, and (e) syphilitic cirrhosis
- 4 Obstructive jaundice from stones or carcinoma of pancreas, or other causes outside the liver

Cases due to the first cause are by far the most common, and comprise the so-called toxic hepatitis group. Stokes has called attention to the influence that various microorganisms may take in the production of this type of involvement. Infectious cholangitis is possibly also associated.

The recent literature has contained references to the value of the so-called hepatic functional tests. To Abel Rowntree, and Rosenthal belongs the credit for developing the test. Piersol and Bockus, Greenbaum and Brown, Chargin and Orgel, Scham-

berg and Brown, Ottenberg, Rosenfeld and Goldsmith, and more recently Snell, Walters, Greene, and Rowntree, have made clinical application and demonstrated the value of the tests. For a detailed description of the technic of the tests and the methods of analysis, the reader is referred to the reports mentioned. It is to be borne in mind that these tests have not as yet reached a point in their development in which they are capable of differentiating the type of liver complication. In other words the tests will not determine the various diseases of the liver, neither will they determine exactly the degree of the impaired function of the liver, because the liver probably has several different functions. The tests, when repeated and observed sufficiently long, do indicate that there is hepatic deficiency, and aid us materially in determining whether the jaundice is merely a symptom of a mild toxic hepatitis, or of a more severe hepatic derangement. One series of tests is not sufficient to warrant conclusions, but several series over a period of several weeks are of decided aid.

Case 1.—The first patient has been under our care for more than seven years. He came to the Clinic because of a Charcot knee joint in 1917. A well advanced tabes dorsalis was recognized. The spinal fluid and blood tests were both positive for syphilis. Under our direction he has received injections of arsphenamin, of the succinimid of mercury, of sodium iodid, and mercurial inunctions during the last seven years. Although the serology became completely negative and had been so for several years, the inunctions were continued because the neurosyphilis was progressive in spite of the negative serology, and because the Charcot joints continued to form until there was a total of seven such joints. Shortly after completing a course of mercurial inunctions in the early part of June, the patient became jaundiced. When he returned to the Clinic, the jaundice was of three weeks' duration. He complained of loss of appetite, lassitude, fatigue, nausea and vomiting. He had noted edema of the ankles during the second week of the jaundice, but this lasted for one week only. The stools were clay colored, and the urine a very dark amber. He had lost 11 pounds. He had no colic, and no masses were palpable in the abdomen although there was tenderness on deep palpitation around the upper right quadrant. The jaundice was of Grade 3 on a basis of 1 to 4. July 7, 1924, the liver functional studies were reported as follows: blood urea 51, uric acid 27, creatinin 28. The blood urea has been between 40 and 45 for the last few years. The serum bilirubin was 17.6 mg., and the van den Bergh test positive, 40 per cent of the phenol tetrachlorphthalein returned at the end of the first hour, and 36 per cent at the end of the second hour. (The normal readings are serum bilirubin 2.0

mg, phenoltetrachlorphthalein is returned up to 8 per cent in one hour, and after two hours there is no return of the dye) July 10, 1924, when the tests were repeated, the serum bilirubin was 9.9 mg, 34 per cent of the dye returned at the end of the first hour, and 26 per cent at the end of the second. The van den Bergh test was positive.

Besides the routine measures used in the treatment of toxic jaundice, such as giving sodium phosphate, one dram three times daily, ovgall and pancreatin tablets, and a soft diet, the patient was given five duodenal lavages at two-day intervals, according to the technic recently described by Wilhelm. At the third lavage there was a free and copious return of golden brown bile followed immediately by very definite relief from symptoms. The fourth and fifth lavages were done at two-day intervals to relieve the symptoms further.

Although the second series of tests indicated improvement, there was but slight symptomatic change until after the third lavage on July 16. The following day the tests indicated further improvement, as evidenced by the reading of 7.6 mg of serum bilirubin, and the recovery of 18 per cent of dye at the end of the first hour, and 10 per cent at the end of the second. Following the successful lavage, the patient felt decidedly better, and the jaundice started to abate. July 26, the jaundice had practically disappeared, there was 4.3 mg of serum bilirubin, 10 per cent of the dye was recovered at the end of the first hour, and 8 per cent at the end of the second. The patient was feeling perfectly well and rapidly regaining the lost weight. Although no signs of jaundice remained, the functional tests continued to indicate slight impairment of function, so slight, however, that it was not considered significant. At the last test, August 25, 1924, the serum bilirubin was 0.8 mg. The dye was not injected because the patient had had nausea, vomiting and backache, one or two hours after the last injection. He had also complained of phlebitis which developed at the site of the injection and extended several inches up and down the median cephalic vein. This latter complication seems to be entirely due to technic, and is not so common or serious as to contraindicate the use of phenoltetrachlorphthalein.

*Comment*—Duodenal lavage, besides being an efficient therapeutic measure for the relief of the symptoms of toxic jaundice, following arsphenamin injections, may at times be of aid in the diagnosis of the type of jaundice. I have not as yet encountered a severe grade of hepatitis in which the duodenal lavage has given any symptomatic relief, but on the other hand, all of the cases of toxic or infectious hepatitis have shown very definite symptomatic and clinical response to the procedure. It may be necessary to give as many as ten lavages before a free return of bile is obtained, following which the patient notes decided relief.

In this case, the first and second functional test reports indicated the presence of hepatic involvement, but the gradual decline in the serum bilirubin of the blood, and the decrease in the amount of the dye returned suggested that the involvement was of the toxic type. This was confirmed by the favorable response to duodenal lavage and the subsequent course of the patient. The improvement indicated by the tests preceded the symptomatic response, and when taken in conjunction offered a good prognostic sign. The last tests, August 25, indicated that the degree of hepatic involvement was not severe enough to stop further treatment for syphilis. Treatment was again started after the jaundice was considerably diminished, apparently it did not hasten the convalescence, or offer any further obstacles.

Hepatic functional tests do not determine the type of hepatic damage, any more than the renal functional tests determine the type of nephritis.

**Case 2**—This patient came to the Clinic in November, 1923, with asymptomatic neurosyphilis. The blood Kolmer reaction was reported as 44—--, and the spinal fluid as 44—--, with positive Nonne and 7 cells. The colloidal benzoin reaction was 002000033200000. The general routine examination otherwise was negative. The patient gave a history of an acute syphilitic infection in 1921. Previous to coming to the Clinic, he had received sixteen intravenous injections of neo arsphenamin, and twenty intramuscular injections of the salicylate of mercury. He had been taking mercury pills for the last sixteen months. The pills were taken at irregular intervals. Under our direction he started treatment November 16, and received seven intravenous injections of arsphenamin (originil) at weekly intervals, the total dosage being 27 gm. In addition, three intraspinal treatments were given according to the Swift-Ellis Ogilvie modification. Five intramuscular injections of bichloridol, 1 grain, at weekly intervals, and ten intravenous injections of 100 c.c. of a 10 per cent sodium iodid solution were also given. The patient was dismissed from the Clinic January 2, and advised to start on a course of forty, 50 grain mercurial rubs. He failed to take the rubs, however, but reported February 4, that he was feeling very well. About February 15 he complained of nausea, loss of ambition and appetite, malaise, and pain in bones and muscles, which persisted until March 15 when the jaundice appeared. The local physician who was called at this time advised an operation for the removal of gallstones. The operation was postponed for six weeks, during which time the jaundice became more intense, and the patient complained more of the nausea, loss of weight, and the constitutional symptoms so common in cases of infectious jaundice. Against our advice the patient was

operated on for cholelithiasis, the diagnosis being based merely on the persistent jaundice. No gallstones were found, the liver was reported to be somewhat enlarged and congested. The patient's convalescence was somewhat protracted, and he remained in the hospital for eight weeks, the jaundice showing no tendency to diminish.

The patient returned to the Clinic June 15, still slightly jaundiced. There was a small amount of free fluid in the abdomen, and very slight edema of the ankles. The stools were still clay colored, and the urine gave a positive reaction for bile. The wound had healed, leaving a small ventral hernia. The reaction on the blood by the Kolmer test was still reported as strongly positive, urinalysis was completely negative. The serum bilirubin was 3.0 mg at the end of one hour, and the patient showed evidence of a slight degree of retention of the phenoltetrachlorphthalein. In view of the functional hepatic tests which were only slightly above normal, and of the prolonged retracted course of the jaundice which suggested a syphilitic factor, the patient was given daily, intramuscular injections of the succinimid of mercury, and a 10 per cent sodium iodid solution intravenously. Within a very few days he reported that he was feeling better, and he continued to improve rapidly. The subsequent hepatic functional tests were as follows:

1924	Serum bilirubin at the end of one hour	Dye retention, per cent	
		One hour	Two hours
June 30	1.84 mg	8	5
July 29	1.35 mg	8	4
November 11	1.21 mg	6	4

*Comment*—This patient presented the symptoms of so-called toxic hepatitis in which the liver functional tests demonstrated late in the course of the jaundice that the hepatic involvement was benign. The evidence of toxic hepatitis was noted at operation. The tests likewise indicated that continued antisyphilitic treatment was not contra-indicated, this was confirmed subjectively and objectively. The jaundice was a manifestation of the toxic hepatitis which, alone in a patient of twenty-six years, without a history of colic, was not sufficient evidence to warrant an exploratory laparotomy. The functional tests indicated quite definitely that the liver had not been very seriously damaged. The fact that the patient showed definite improvement after treatment with mercury succinimid was instituted would suggest that the mild hepatitis was possibly of syphilitic origin. On the other hand, it has been our experience that the toxic hepatitis which appears following treatment for syphilis is not materially influenced by continued treatment after

the jaundice has developed. This is one reason why we believe that in all cases in which icterus develops following the administration of arsphenamin and mercury, we are not justified in attributing the icterus to the treatment, or to the syphilis alone.

The patient's wife, who came with him at the time of his original examination, underwent a much more drastic course of treatment without any serious or embarrassing complications. This might imply that this couple did not harbor a special strain of spirochete, which displayed a particular affinity for hepatic tissue, particularly since the wife presented an acute papular syphilitic of the skin, and we know that it is not unusual to find acute hepatitis as a complication of acute syphilis, resulting from the spirochetemia.

The patient has completed a course of mercury inunctions without discomfort, and has recently completed his third course of arsphenamin without incident. The hepatic tests nine months after the onset of the jaundice apparently indicated a definite return of hepatic function to normal.

**Case 3** — This patient, aged forty-six years, came to the Clinic June 10, 1923, with a complaint suggesting cholelithiasis. He gave a history of previous attacks of colic.

The reaction was positive for syphilis in a series of tests on the blood by the Kolmer technic. It was decided to have him undergo a thorough course of treatment for syphilis before operating, because in our experience, gummatous hepatitis has at times simulated gallstone disease. At the completion of a course of six arsphenamin injections (old), the total dosage being 2.8 gm., twenty nine intramuscular injections of the succinimid of mercury,  $\frac{1}{6}$  grain each, and twenty five intravenous injections of the 16 per cent sodium iodid solution of 100 c.c. each, he was operated on August 8, 1923. Stones were found in the gallbladder, and there was also definite hepatitis, which was reported as syphilitic. The patient was sent home August 25, and instructed to take a course of forty mercurial rubs. When the rubs were stopped, he had a mild attack of jaundice without colic. He returned November 10, 1923, and received five intravenous injections of arsphenamin, a total dose of 2.1 gm. During this course he was slightly jaundiced, and complained somewhat of nausea, malaise and lassitude. The jaundice, however, cleared up, but recurred twice before he left for home, January 4, 1924. February 15, he developed all the symptoms of severe jaundice. It may be said at this point that the amount of treatment he received early in the first course was considerably more intense than it is our custom to give pa-

tients who present evidence of syphilitic hepatitis, because in our experience the liberal use of arsphenamin early in the course of treatment is frequently attended with unfavorable results. On the other hand, if the patient is prepared with a mercurial and iodid course for several months before starting the arsphenamin, the results, although slower, are as a whole much more satisfactory. The process that occurs in the liver as a result of the intensive use of the arsphenamins early in the course of treatment may be a Herxheimer or flaring up of the hepatitis, or a very rapid healing with fibrosis that does not permit of the regeneration of sufficient hepatic tissue to function properly. Mann is of the opinion that the regenerative ability of the liver is almost 100 per cent in the normal liver tissue, although in the diseased liver with decreased blood supply the reaction is less rapid and complete.

The patient returned to the Clinic May 5, having been jaundiced since February 15. The hepatic functional tests, at this time, were reported as follows: serum bilirubin 9.7 mg., van den Bergh direct test positive, dye retention of 36 per cent at the end of the first hour, and 26 per cent at the end of the second. In the duodenal contents the return was 81 of the dye as compared with the normal of 20. The blood urea was 32, the uric acid 3.8, and creatinin 1.9. Five duodenal lavages were given with only slight symptomatic relief following the last two, when there was a moderate flow of bile. However, the degree of jaundice was not materially changed by the drainage.

May 26, three months after the onset of the third attack of painless jaundice, the hepatic tests were reported as follows: serum bilirubin, 9.4, positive van den Bergh test with a retention of dye of 25 per cent at the end of the first hour, and 24 per cent at the end of the second hour. The blood urea was 26 mg., uric acid 3.2, and the creatinin 1.0, which indicated some improvement. The jaundice was still moderate, but the patient continued to have nausea, malaise, lassitude, and loss of appetite. He had lost 18 pounds in weight since the onset of the attack. May 26 he was given intramuscular injections of succinimid of mercury,  $\frac{1}{8}$  grain daily, and intravenous injections of 10 per cent solution of sodium iodid, increasing up to 100 c.c. The clinical improvement from then on was very rapid, and twelve days after starting the mercury and iodid the jaundice was hardly perceptible, and the symptoms of which he complained had disappeared. Blood urea was 25, the uric acid 2.4, creatinin 1.4, serum bilirubin 6.4, van den Bergh positive, a dye retention of 14 per cent the first hour, and 13 per cent the second, which indicated that even though all clinical signs of the jaundice had subsided, the liver was still definitely impaired. The patient returned home and felt well for two months, when he again showed evidences of icterus. The local physician thought that probably a small stone was causing the obstruction and the jaundice. However, the icterus quickly subsided following a course of mercurial rubs, and there has been no further trouble.

*Comment*—A patient with gallstones and hepatitis was placed on treatment for asymptomatic neurosyphilis. At the time of operation, following the first course of treatment for

syphilis, it was found that he had a syphilitic hepatitis. The slightly enlarged liver was recognized previous to the starting of the treatment, but it was thought to be associated with the cholelithiasis and cholecystitis. It is justifiable to assume that the recurring attacks of jaundice after the treatment was stopped were the result of either hepatorecurrence or a fibrosis that had taken place too rapidly. Each time the treatment was stopped, the jaundice recurred, only to disappear when treatment was again started. The hepatic functional tests revealed definite impairment of function before and after treatment, as evidenced particularly by the retention of the dye. The variations in the three series of tests, done before treatment for the syphilis was started, were so slight that they were not significant. The results of the test after the jaundice had subsided indicated that the function of the liver was still definitely impaired, and this was borne out by the third attack of jaundice after the patient's return home. Not only does this case demonstrate the value of the study of function of the liver, but it also emphasizes the fact that all jaundice that appears after treatment for syphilis is not the result of the drugs used, and that other factors such as syphilis or the result of syphilis may contribute.

**Case 4**—This woman came to the Clinic in November, 1923, with a recurring jaundice of seventeen months' duration. The liver was nodular and firm, and it was palpable almost halfway down to the umbilicus. The edge of the spleen was slightly palpable. The patient had lost 20 pounds in weight during the illness, and the jaundice was of the dark, muddy yellow color. The blood Kolmer reaction was 44—. Other findings of note were Urobilin and urobilinogen were present in the urine, which was otherwise negative, the hemoglobin was 61 per cent, the erythrocytes numbered 3,890,000, the leukocytes 7,400, lymphocytes 22 per cent, large mononuclears 4.5 per cent, transitionals 2.5 per cent, neutrophils 69 per cent, eosinophils 1 per cent, basophils 1 per cent. The coagulation time by the Boggs method was eight minutes, and the bleeding time two and one half minutes. Roentgenograms of the chest, stomach, and gallbladder were negative.

In view of the clinical evidence of severe hepatic involvement, the patient was placed in the hospital for preparatory treatment. Tests of the function of the liver, made November 26, showed a serum bilirubin of 13.1, a return of 26 per cent of the phenoltetrachlorphthalein in the first hour, and of 23 per cent at the end of the second. In the hospital the patient was placed on mercury with chalk, 1 grain, three times a day, and increasing doses of the potassium iodid up to 25 minims three times a day. This was con-

tinued for two weeks when she was given 33 grains of mercurial inunction with larger doses of the iodids. One month later the intravenous use of neo-arsphenamin in doses ranging from 0.4 to 0.6 gm for six doses was given December 19, the serum bilirubin was reported as 10 mg, the phenoltetra-chlorphthalein test was not made. At the time of the patient's dismissal, January 24, the serum bilirubin was 2.0, and the recovery of the dye 3 per cent the first hour, and 2 per cent the second. The jaundice had faded considerably, but the edge of the liver was still palpable. The patient felt decidedly better and gained 12 pounds in weight. She was sent home on the 1-grain doses of mercury with chalk, and reported that on March 15, the jaundice had entirely disappeared. She returned to the Clinic April 15, had gained 7 more pounds in weight, and was symptomatically free. The serum bilirubin was 4.8 mg. 25 per cent of the dye returned at the end of one hour, and 20 per cent at the end of the second. This indicated that the hepatic involvement which was apparent when the patient left the Clinic four months before, was still present, in spite of the fact that she was feeling considerably improved. There was no appreciable change in the edge of the liver. Rather than risk the danger of arsphenamin treatments, she was sent home on 25-grain inunctions (one-half cake mercurette) and potassium iodid up to 50 grains three times daily.

August 19, she was further improved clinically. The edge of the liver was not palpable except in the epigastrum, the spleen was readily palpated. The serum bilirubin had increased to 9.2 mg, and the dye retention was 26 per cent for the first and second hours. In spite of the fact that the patient had improved clinically on the mercurial inunctions, I felt that the decrease of the hepatic function as indicated by the tests was the result of the replacement process that was going on in the liver, and that the cautious use of arsphenamin was again justified. She was given six injections (0.3 to 0.6 gm) of neo-arsphenamin at weekly intervals, without complications, except a slight increase in the tint of the icterus in the sclera following each injection. September 11, the serum bilirubin was 5.0 mg. September 26, the serum bilirubin was 4.2 mg and the dye retention 20 per cent the first and second hours. The patient was feeling very well and weighed 120 pounds practically her normal weight.

*Comment*—In this case, the improvement in hepatic function, as indicated by the tests, was not in proportion to the clinical response. Further observations and functional studies will be necessary to determine the results of treatment, and the value of tests of hepatic function during treatment. The advisability of the slow, cautious use of arsphenamin is again emphasized, as are the results of the use of the mulder mercurial preparations in the treatment of syphilis of the liver. The patient at no time showed clinical evidence of too rapid healing such as anasarca or edema of the lower extremities. Nor has there as yet been

evidence of the establishment of collateral circulation on the abdominal wall, which usually follows the healing of extensive hepatitis

TABLE 1  
LABORATORY FINDINGS

Case.	Date, 1924	Serum bilirubin mg	Per cent of phenoltetrachlorphthalein	
			After one hour	After two hours
1	7/7	17 6	40	36
	7/10	9 9	34	26
	7/17	7 6	18	10
	7/26	4 3	10	8
	8/25	0 8		
2	6/16	3 0	Slight reten- tion	Very slight
	6/30	1 84	8	5
	7/29	1 35	8	4
	11/11	1 21	6	4
3	5/5	9 7	36	26
	5/26	9 4	25	24
	6/7	6 4	14	13
4	1923			
	11/26	13 1	26	23
	12/19	10 0		
4	1924			
	1/24	2 0	3	2
	4/15	4 8	25	20
	8/19	9 2	26	26

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## THE CURE OF SYPHILIS

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We have as yet no clinical or laboratory means to determine whether or not an individual is cured of syphilis. That cures occur either through the immunity mechanism alone, or with the aid of treatment, there is no doubt. In the light of our present day knowledge, however, reports of cures by older authorities cannot be accepted. A patient cannot be said to be cured unless evidence of the infection cannot be demonstrated serologically, clinically, or at necropsy. Even reinfection is no longer regarded as positive evidence of a previous cure. The term "superinfection" is probably, therefore, more appropriate in most instances when a patient presents the syndrome of a primary lesion, a secondary eruption and the other manifestations of the early stages of infection for a second or third time.

The varied course of syphilitic infections in different individuals stimulated careful observers, many years ago, to speculate on the mechanism involved in the cure of syphilis. Such speculations were, of course, entirely inaccurate so long as the relationship of late neurosyphilis, vascular and other later visceral injuries to the early infection was not fully established. Even now, it must be admitted that there are imperfections in the means we have devised to explain the various courses which the disease may pursue.

The presence of an inherent defense mechanism can no longer be doubted. An understanding of this has been chiefly brought about by careful study of large amounts of clinical and necropsy material, and will continue to be furthered by such observations in the future. The laboratory has added but little to our conception in this regard, because the defense mechanism in syphilis is dependent on sessile receptors.

It is likely that the course of an infection is dependent on three main factors (1) the initial quantity and quality of the infecting virus, (2) the biologic relationship between the parasite and body cell, and (3) the treatment.

The degree of saturation with spirochetes in individual localities is partly a matter of chance. The distribution to the various organs is, however, more abundant and profuse, the less the resistance of the body cells, and the greater the fecundity of the virus. It is not surprising that the skin should be well supplied early with spirochetes, owing to its large expanse. According to Bloch, Hoffmann, Gennerich and others, it is in the skin that the battle for supremacy between the infecting organism and the host is chiefly fought, and either lost or won. Every syphilographer is familiar with patients who give a classical history of infection with an abundant secondary eruption in whom no trace of the disease can be found decades after the infection. Just as familiar is the patient who sincerely denies having the least knowledge of secondary skin manifestations, when, in later life, he is confronted with syphilis of the cardiovascular or nervous system.

Paradoxically it seems to be a fact that malignant syphilis, when associated with skin lesions, is in reality benign. In the greater number of cases, recovery is complete under judicious treatment.

It is likely that the comparatively benign course of syphilis noted in primitive as compared to civilized peoples is explainable by the difference in the virulence of the organism attacking a comparatively virgin soil unmodified by treatment. The predominance of gummas in the skin and bones, and the striking absence of involvement of the vascular and nervous systems is an acknowledged fact. The American negro is not a case in point, however, since he has long had the benefit of treatment.

The benign course observed in primitive tribes may, however, be partly explainable by intercurrent infections such as malaria, which seemingly have a decided influence on the defense mechanism. The precocious tertiary stage in which the disease runs its course in a few months has repeatedly been held out as a specter

against inadequate treatment. Such cases are seen but rarely, and while they may prove disastrous, it is doubtful whether they might not be regarded much as malignant syphilis is regarded, as essentially benign. The term "immunity," as applied to patients who have had small-pox, or been successfully vaccinated, is probably never justifiable as applied to syphilis. Late in the infection, the patient develops a hypersensitiveness, often referred to as "allergy," and the foregoing considerations make it seem likely that this part of the immunity mechanism resides chiefly in the skin. Hoffmann would like to assume a special ferment action in the skin, which he terms "esophylaxis." It is possible that spontaneous cure is dependent on this peculiar cutaneous phenomenon.

The opinion that the blood is not the direct carrier of immune bodies seems to gain negative support from the observations that neither the serum of a patient just recovering from an attack of secondary syphilis, nor that of a patient with old latent syphilis, nor the serum of naturally immune animals, has any obvious curative effect on acute syphilis. Neither do such serums have any deleterious effect on the *Spirochete pallida* *in vitro*. The same may be said of the serum and cerebrospinal fluid of patients with old neurosyphilis.

That treatment decidedly influences the course of the infection seems to be proved. While the proof of cure is not yet fully accepted by the conservative observer, and requires the observation of large numbers of patients for decades to come, there is sufficient evidence to point strongly to the probability of cure by treatment. It is admitted that syphilis may be cured by the patient's own defense mechanism. But usually such a cure is only obtained after considerable injury to the vascular system, often to the smaller vessels. In such cases the clinical signs may remain long in abeyance, and only at necropsy are revealed degenerations of much greater extent than was ever suspected even by painstaking clinical examination. Theoretically it has been assumed that if arsenicals are systematically used, but do not kill all the spirochetes in a treated person, the physiologic defense mechanism is never aroused, and he is

left completely without protection. Practical observation does not seem to bear out this theory. Patients are often seen who have had inadequate treatment according to our present day conception. Years after, such patients may have a positive Wassermann reaction on the blood without clinical evidence of involvement of the central nervous system, or the grosser components of the vascular system, and there may be manifestations of allergy in the form of gummatous lesions in the skin, mucous membranes, and bones, which would indicate the presence of a true allergy. Certain authorities believe that since the advent of chemotherapy in the form of arsenicals, neurosyphilis has been on the increase. At present it must remain doubtful whether such increase is a fact, or whether more modern methods of observation, including the frequent employment of the spinal fluid test, will permit the correct diagnosis of cases such as were formerly overlooked. This problem is one of supreme importance, and merits intensive study in the future. It can probably be settled only by careful observation of a large clinical material over many years.

The valuable Wassermann test occupies so prominent a place in the minds of many practitioners as a guide to diagnosis and cure, that emphasis cannot be laid too forcibly on its defects. Its relative importance can be readily understood if it is remembered that the reaction is very likely the result of a destructive action of the spirochete on certain body tissues. If, then, such activity is temporarily inhibited by some of the factors considered in previous paragraphs, a negative Wassermann reaction does not necessarily mean an elimination of the infecting virus, but may mean only its reduction in activity to the point where not sufficient débris is produced to be measurable by the serum test. A positive Wassermann reaction means syphilis, with rare exceptions, a persistent positive reaction after treatment probably means the rather active progress of syphilis, notwithstanding various speculations to the contrary. A negative Wassermann reaction does not mean absence of syphilis, it may mean temporary cessation of appreciable destructive effects of the *Spirochete pallida*. As illustrative of many of the

foregoing considerations, I wish to present the following case

The patient was seen at the Mayo Clinic for the first time in February, 1918, at the age of forty-nine years. He had a primary lesion on the penis, but there was no evidence of secondaries. Repeated dark-field examinations of the lesions did not reveal *Spirochete pallida*. The Wassermann reaction on the blood was positive, however. This was thought to be a favorable case for abortive cure. Under systematic treatment for syphilis, the lesion promptly involuted, and the Wassermann reaction became negative. Frequent observations did not disclose evidence of the disease, and the Wassermann reaction remained persistently negative (Tabulation). In June, 1924, the patient returned, complaining of malaise for which no definite cause could be found. A Wassermann reaction and spinal fluid examination were negative. A month later he again returned complaining of the same feeling of malaise, this time a definite gumma was found on the left soft palate, and the Wassermann reaction was strongly positive. Under the usual treatment for syphilis the gumma promptly involuted, and the malaise disappeared. A spinal test taken during the gummatous stage was entirely negative.

#### COMMENT

This patient's history illustrates that although a case may seem favorable for an abortive cure, there is no positive assurance of such a result even with adequate treatment. A Wassermann reaction persistently negative for more than five years does not necessarily mean a cure. Treatment evidently does not rob the patient of his physiologic defense, since this patient showed definite evidence of allergy in the form of a gumma, and there was no evidence of syphilitic involvement of the visceral or central nervous system. The Wassermann reaction became promptly negative under treatment, and remained so until a destructive lesion appeared, when it again became strongly positive.

## TREATMENT BEFORE APPEARANCE OF GUMMA

Date.	Arseno-benzoI-arsphen-amin, intra-venously, gm.	Mercury inunction.	Date.	Comple- ment fixation	Date	Cerebrospinal fluid.
3/5/19	0.3	A total of 276 mer-	3/1/19	Weakly positive	1/31/20	Wassermann, nega-
3/11/19	0.4	curettes of Parke	3/4/19	Strongly positive		tive.
3/15/19	0.4	Davis type, from				Nonne, negative
3/19/19	0.5	2/28/19 to	3/27/19	Negative		Cells, 9
3/26/19	0.5	7/16/21	4/4/19	Negative		
4/2/19	0.5		6/20/19	Negative		
4/9/19	0.5		8/8/19	Negative.	12/21/20	Wassermann, nega-
4/16/19	0.5		9/19/19	Negative		tive.
8/16/19	0.3		1/23/20	Negative		Nonne negative.
8/23/19	0.4		2/23/20	Negative		Cells 3
8/30/19	0.4		6/12/20	Negative.		
9/6/19	0.4		11/27/20	Negative		
9/13/19	0.4		8/1/21	Negative.	6/9/24	Wassermann nega-
9/20/19	0.4		1/26/24	Negative.		tive.
1/24/20	0.3		5/26/24	Negative		Nonne, negative
1/31/20	0.4		6/26/24	Negative		Cells, 1
2/7/20	0.4					
2/16/20	0.5					
2/21/20	0.4					
Total	7.9 (19 injections)					

## EARLY CARE OF CROSS-EYED CHILDREN

AVERY D PRANGEN

The early care of cross-eyed children is a problem concerning which the medical profession, as a whole, is very poorly informed. This is unfortunate as the family physician is usually the first to be consulted. As in all incipient diseases, it is imperative that correct measures be instituted at once to prevent disastrous sequelæ.

Concomitant convergent or divergent strabismus has its onset in infancy or early childhood, usually before the age of six. The onset may be insidious or abrupt, and often follows trauma, as from a fall, or illness, such as measles. The disturbance is characterized by one of the eyes turning in or out. It may be always in the same eye, or the eyes may alternate in crossing. Rarely do both eyes deviate at the same time. In some cases the squint is constant, in others it appears only when the child is ill or tired. The latter cases are the ones usually overlooked or neglected, under the impression that the occasional squinting is of no consequence. On the contrary, this is the stage when treatment is most efficacious.

There are a number of factors which play an important part in the production of strabismus in children. These may be divided into primary and secondary, or precipitating causes. The primary causes are (1) defective fusion sense, (2) uncorrected errors of refraction, particularly anisometropia or inequality of refraction in the two eyes, and (3) poor vision from any cause. The secondary factors are those which, when primary defects exist, precipitate the onset of the strabismus. These are (1) a disturbance of physiologic equilibrium by any cause undermining the general health either acute or chronic, and (2) physical trauma such as a bad fall or bump.

Does the fact that he is cross-eyed have any effect on the child himself? Emphatically yes. Such a child is indeed an under-privileged child. Due to his obvious physical deformity his whole mental make-up is seriously affected. He becomes timid, introspective, diffident, hypersensitive, and shrinking. Such characteristics hamper him in his association with others. He cannot develop those traits of mind so essential to the mastery of his environment. It is but a preliminary step to the establishment of an inferiority complex so disastrous in adult life. If allowed to go into adult life uncorrected, the physical deformity furnishes an unfair handicap socially and in the business world. Physically, also, the nervous system of the child can be seriously undermined by the strain of carrying the load of an uncorrected error of refraction.

The most serious result of improper treatment or neglect of the strabismic child is the development of amblyopia exanopsia, or partial blindness from disuse. Given the primary factors for the onset of strabismus, nature soon gives up the excessive effort necessary for the simultaneous use of both eyes, and concentrates on the use of only one eye. This is the path of least resistance. Then, because the squinting eye is not being used, the visual centers for that eye do not receive the stimuli necessary for their development. In the young child, if this state of affairs is allowed to exist, useful vision is soon lost in one eye. The younger the age at the onset of strabismus, the more rapid the development of amblyopia. Worth says that a child of six months, affected with strabismus, becomes amblyopic in from eight to ten weeks, one of eighteen months, in from five to six months, one of three years, in one year, while one of six years will probably not become amblyopic. In other words, the visual centers are either properly developed by the age of six, or they never will develop. It is perfectly plain, then, that treatment for strabismus should be started at the onset. If treatment is delayed until the age of six or later, there is a very great probability that the child will go through life with one partially blind, useless eye.

Another local complication resulting from improper early

treatment of strabismus is the production of primary insufficiencies, and secondary contractures of the extra-ocular muscles. These are the result of long continued improper position of the eyes. When once firmly established, these changes in the muscles materially lessen the chances for a nonoperative cure. Also they make operative procedures more difficult and uncertain of success.

The keynote in the treatment of these children is immediate attention, in order to prevent amblyopia exanopsia. It must be borne in mind that the younger the child, the more rapid is the onset of amblyopia, also that the visual centers for both eyes and the fusion sense will be developed by the age of six, if they are to be developed at all. There are two factors in the accomplishment of this purpose (1) the child's vision in the two eyes must be made as nearly equal as possible by keeping both eyes in use. Two dissimilar images are not compatible with fusion, the poorer image will be ignored or suppressed. (2) Good vision in each eye demands the proper correction of existing errors of refraction, and inequality of refraction, anisometropia. Any pathologic condition causing obstruction of vision such as juvenile cataracts, should also be remedied. In young children refraction can only properly be done by a well trained ophthalmologist using the retinoscope after instilling a cycloplegic in the eyes to relax the active accommodation. Correcting lenses should be at once prescribed and constantly worn. Practically all manageable children more than two years of age will wear glasses. With the adjustment of proper lenses there is often immediate improvement in the strabismus and the eyes straighten within a few months. This indicates that the refractive errors, with attendant poor vision and strain of the eyes, were the cause of the extra-ocular imbalance. It is often surprising how slight and inconsequential the refractive error may be and yet cause strabismus, in such cases the strabismus disappears immediately when lenses are worn. These errors, though small, seem sufficient to upset the muscle balance and fusion sense which probably were already below par.

Strabismic children under two years of age, or older children

wearing glasses, who continue to deviate one eye should be compelled to use this eye a part of each day. A weak solution of atropin may be used in the good eye to blur the vision, thus forcing the use of the poorer one, or the good eye may be padded or bandaged several hours each day. If glasses are worn, an opaque shield can be hooked onto the frame over the lens of the good eye. Accident can be avoided if the child plays about home under the close scrutiny of the parents. Very soon it will be observed that the child uses the poorer eye readily and without awkwardness, due to improvement in the vision. These measures are, of course, unnecessary if the squint is an alternating one, for then one eye is used as much as the other. However, even in the presence of alternation, amblyopia may develop if glasses are not worn to correct the refractive error and anisometropia due to the poor vision in one eye. Amblyopia is often noted in older children without strabismus.

Inasmuch as a defective fusion sense is one of the main factors in the production of strabismus, an attempt should be made to strengthen this defect. In order to do this, one must be able to keep the child under observation during treatment. Fusion exercises, like prism exercises, need professional supervision, for if not done correctly their effect is nil. Numerous ingenious devices can be used, such as the Worth amblyoscope, and even the old-fashioned family stereoscope. The child is encouraged to fuse the two images of familiar objects, taken at slightly different angles, and the sense of perspective is thus stimulated. Much can be accomplished by co-operation of the parents and adherence to daily routine.

The insufficiencies and contractures seen in older children affected with strabismus are, I believe, usually due to earlier improper management. By the early use of the corrective measures here outlined, these extra-ocular muscle defects could be greatly mitigated or entirely avoided.

#### CONCLUSIONS

I believe that if proper treatment were instituted at once, and strictly adhered to, in all cases of early strabismus in children

(1) permanent cures would soon be brought about in many cases, thus removing a terrible handicap from these unfortunate children, (2) the curse of amblyopia exanopsia would be practically abolished, except in those few instances in which it is congenital, (3) in only a small percentage of children would it be necessary to correct the strabismus by operation, and (4) when operation is indicated it could be more effectively and successfully performed



## THE OPHTHALMOLOGIC FINDINGS IN CASES OF MULTIPLE SCLEROSIS: A STUDY OF 100 CASES

JOHN F. GIPNER

An ophthalmologic study of every case of multiple sclerosis is important, since in approximately 50 per cent of such cases the optic nerve is affected. This affection is particularly important because it is often an early manifestation of multiple sclerosis, and may even precede any other for from one to two years.

Kollner says that more than half of all cases of acute retrobulbar neuritis with no explicable cause, later develop symptoms of multiple sclerosis. In many instances, after a careful neurologic investigation, which should never be neglected in any case of this type, obscure signs are found which alone have no significance, but which, considered with the optic nerve process, permit the recognition of multiple sclerosis even at a very early stage. The fundus should be examined in undoubtedly cases of multiple sclerosis, for even in the absence of any visual disturbance the optic disc may show a characteristic pallor, the result of a previous active process in the nerve.

Textbooks have emphasized the presence of temporal pallor of the nerve head on ophthalmoscopic examination of the fundus in cases of multiple sclerosis. This picture, however, has been noted but rarely in a routine examination of the fundus in such cases in the Mayo Clinic. In a series of 100 cases the discs of only eleven of 200 eyes were found to have a definite temporal pallor, and there was only a suggestion of temporal pallor in ten eyes. There was usually a generalized pallor of the discs. This was noted in seventy-three eyes, in only fourteen of these, however, was there a loss of nerve substance due to atrophy of the nerve fibers.

The ophthalmoscopic picture of multiple sclerosis depends on the location of the inflammatory lesion in the optic nerve.

If the focus is in the orbital or intracranial portion, retrobulbar neuritis results. An extreme diminution of the visual acuity, and even acute blindness may be present, while the appearance of the fundus is entirely negative. Should the focus of the disease be near the nerve head, there may be hyperemia of the disc. If it is in the nerve head, optic neuritis with blurred disc margins, elevation of the disc and distended veins result. Kollner says that the edema does not spread so far into the surrounding retina as it does in cases of retinitis of nephritis, or in cases of syphilitic neuroretinitis. Optic neuritis with multiple sclerosis is rare, it was not present in any of the cases in this series. Uhthoff, on the other hand, found five in a series of 100 cases. Frank has reported two cases of choked disc in a series of seventy-one. Usually, as in our series, only the results of previous involvement of the optic nerve in the form of secondary changes were seen.

In this series general pallor without loss of substance was seen in fifty-nine eyes, it was bilateral in twenty-two cases and unilateral in fifteen. General pallor with loss of substance or simple optic atrophy was present in fourteen eyes, bilaterally in four cases and unilaterally in six. Definite temporal pallor was present in eleven eyes, bilaterally in three cases and unilaterally in five. Temporal pallor was only suggestive in ten eyes, bilaterally in three cases and unilaterally in four. The pallor of the disc resulting from the descending atrophy in cases of multiple sclerosis differs from that of the tabetic type of atrophy in that the pallor with tabes is practically always bilateral, whereas with multiple sclerosis it is unilateral in almost half of the cases. Tabetic atrophy is gradual and loss of vision progressive, while with multiple sclerosis loss of vision is often sudden, with a fairly rapid return of the peripheral fields, and only a relative or absolute central scotoma remaining, or else with no demonstrable change in the field.

Involvement of the optic nerve may be chronic and gradual, sudden, as in acute retrobulbar neuritis, or chronic in any degree between these extremes. Patients with acute retrobulbar neuritis, and sudden loss of vision usually regain their peripheral

visual fields in a few weeks, and may, or may not, have permanent central scotomas. The fundus is usually normal, although a mild hyperemia may be present. In the slowly progressing type the visual disturbance develops along with the partial pallor or atrophy of the optic discs.

The visual acuity in cases of multiple sclerosis, however, does not always agree with what would be anticipated from the ophthalmoscopic findings. In ninety-four eyes with changes in the appearance of the discs there was good vision in forty-eight, and poor vision in thirty-nine (Table 1). In 103 eyes

TABLE 1  
VISUAL ACUITY IN 100 CASES OF MULTIPLE SCLEROSIS

Disproportion between vision and appearance of optic disk.	Eyes.	Eyes with good vision, 6/10 or more.		Eyes with poor vision, 6/12 or less.		Vision not recorded eyes.
		Bi-lateral.	Uni-lateral.	Bi-lateral.	Uni-lateral.	
General pallor without loss of substance	59	16	17	14	8	4
Simple optic atrophy	14	2	4	4	1	3
Definite temporal pallor	11	2	1	4	4	
Suggestion of temporal pallor	10	2	4	2	2	
Abnormal discs	94	22	26	24	15	7
Normal discs	103	64	24		8	7
Total discs	197*	86	50	24	23	14

\* Condition of three eyes not tabulated (bilateral retinitis proliferans and a unilateral excessive myopia).

with normal fundi the vision was poor in eight, and could not be improved by glasses in one, there was a relative central scotoma. This disproportion between the vision and the fundus picture is characteristic of multiple sclerosis. It is explained by the fact that there is but slight tendency to descending atrophy, so that the presence of retrobulbar foci is not made manifest in the fundus, and by the additional fact that when the sclerotic foci are examined microscopically, there is either complete or partial preservation of the axis cylinders, by which the conductivity of the nerve fibers is retained to a greater or less ex-

tent. Thus we may find in the stage of acute retrobulbar neuritis, normal fundi with marked reduction of the visual acuity, and later, the exact opposite, when the process has healed, that is, good vision with marked changes in the disc.

Just as it is impossible to estimate the visual acuity by the appearance of the fundus, it is impossible to anticipate the presence or absence of a visual field defect. Thus disproportion be-

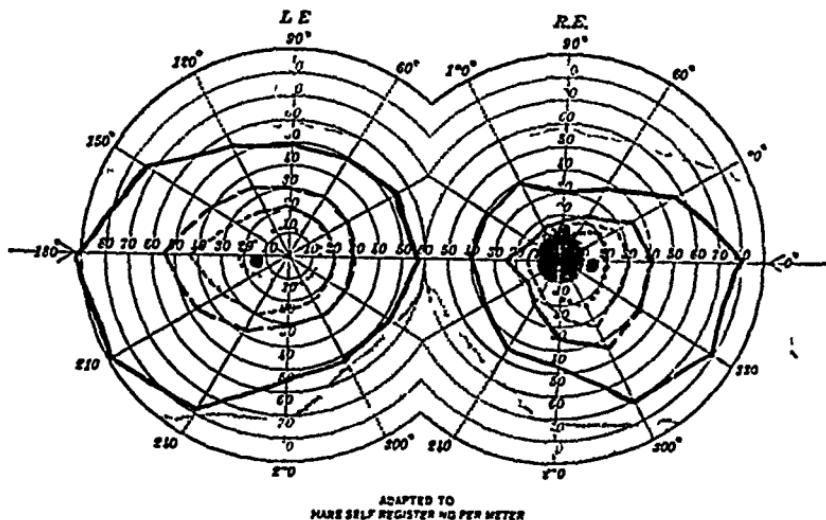


Fig. 195 (Case 1).—Typical perimetric visual fields found in a case of multiple sclerosis. Vision right eye 1/60, left eye 6/6, pupils and reflexes normal, simple optic atrophy of right eye, left fundus negative. Mild peripheral contraction and absolute central scotoma of right perimetric field, left field normal.

tween the appearance of the fundus and the field defect is another characteristic finding in cases of multiple sclerosis.

As the inflammatory focus may be located in any part of the optic nerve, chiasm or tract, almost any type of field defect may be found. Uhthoff reported a case of ring scotoma in multiple sclerosis. The most common defect of the visual field is a central scotoma for form and colors, either relative or absolute (Figs. 195, 196).

The visual fields were tested in all our cases by a rough method. Perimetric fields were taken if these showed changes

Central fields were taken in all cases in which the vision was not improved by glasses. Of the nineteen cases with charted fields, relative central scotomas were present in five cases, bilaterally in two, and unilaterally in three. Concentric contraction of the visual fields for form color was found in three cases, in one of which the defect was bilateral. There was unilateral concentric contraction for colors alone in one case. Bilaterally enlarged blind spots were present in one case (Table 2). In one case there were bilateral absolute central scotomas, which were continuous with the blind spot (Figs 197, 198).

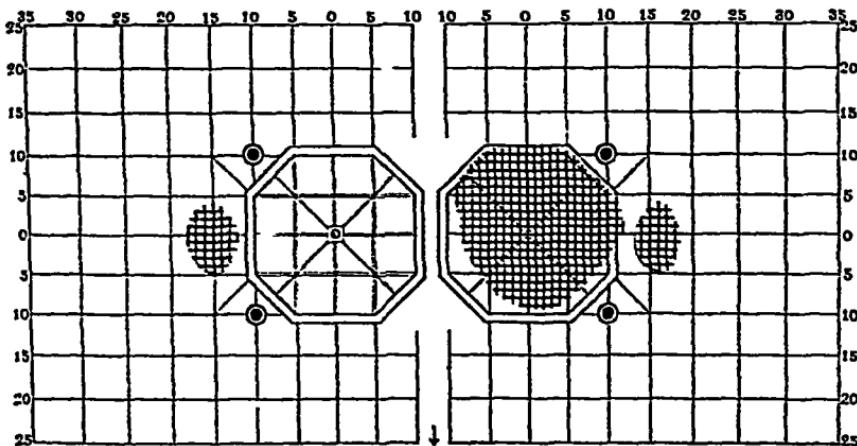


Fig 196 (Case 1) —Central field changes, showing absolute central scotoma of right eye

All the central scotomas occurred in young persons from twenty to thirty-five years of age, and represented the severe, acute retrobulbar type of lesion with marked loss of visual acuity (Table 3). One would expect that in the cases of central scotomas which must be due to changes in the papillo-macular bundle fibers, there would be definite temporal pallor. In but one case in this series in which the visual field showed an absolute central scotoma was there a definite temporal pallor of the disc. Two fields with relative central scotomas, and one with an absolute central scotoma, were found in eyes with a suggestive temporal pallor of the discs.

TABLE 2  
VISUAL FIELD DEFECTS IN NINETEEN OF THE 100 CASES OF  
MULTIPLE SCLEROSIS

Disposition between field defects and appearance of optic d.c.	Concentric con- traction.		Central scoto- ma.		Blind spots	
	Per- ipheral fields	Color fields.	Rela- tive	Absolu- te	Nor- mal	En- larged
General pallor without loss of substance	1		7	4*	8	2
Simple optic atrophy	3		4	1	8	
Definite temporal pallor				1	1	
Suggestion of temporal pallor			2	1	3	
Normal discs		1	1		2	
Total visual field defects	4	1	14	7	22	2
Bilateral field defects	1		5	2		2
Unilateral field defects	2	1	4	3		
Total number of cases	3	1	9	5		1

\* One case with bilateral absolute central scotoma continuous with blind spots.

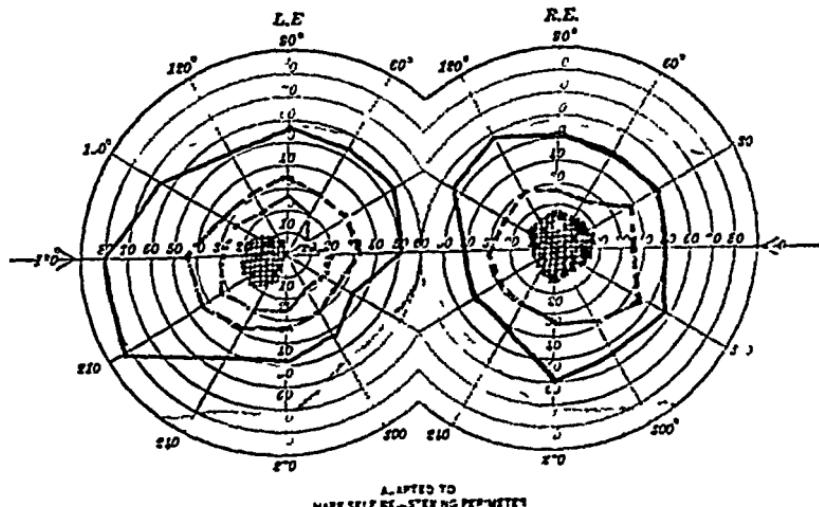


Fig. 197 (Case 2).—Atypical visual fields found in case of multiple sclerosis. Vision of right eye sufficient to count fingers, left eye 6/60 pupils and reflexes normal, generalized pallor of both discs of fundi with no loss of substance. Moderate peripheral contraction of right form field with absolute central scotoma with no field for red or green, slight contraction of left form field with no field for green, and with absolute central scotoma, continuous with blind spot.

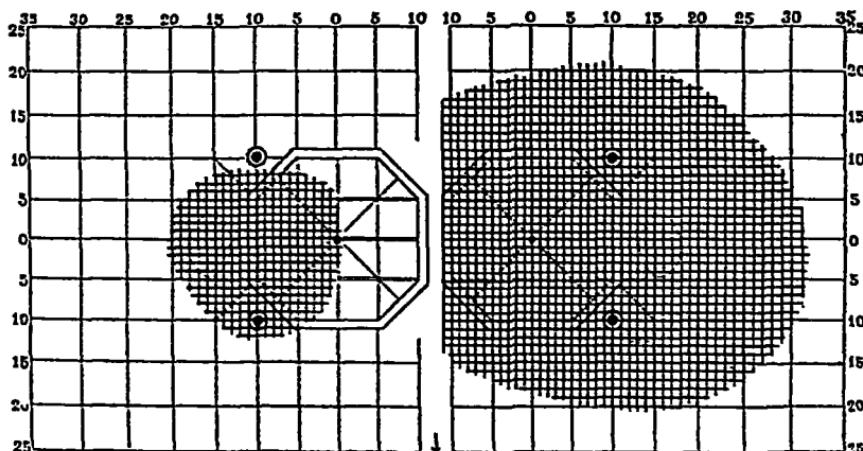


Fig 198 (Case 2) —Central fields, showing the absolute central scotoma continuous with blind spot, with partial preservation of nasal portion of left macular field

TABLE 3

AGES OF PATIENTS WITH MULTIPLE SCLEROSIS

Years.	Cases.	Males.	Females
10 to 20	2		2
21 to 30	34	18	16
31 to 40	53	28	25
41 to 50	10	5	5
51 to 60	1	1	
Total	100	52	48

Nystagmus was also found in thirty-two cases. This was horizontal in two cases, vertical in two, combined in twenty-seven, and rotary to the left in one.

The pupils revealed nothing of importance. The right was larger than the left in nineteen cases, the left larger than the right in nine, they were irregular in twelve. The light reflex was reduced in nine cases, and the reflex of contraction in convergence was reduced in three. Concerning the muscular anomalies little need be said. Convergence was poor in two cases.

There was a partial conjugate paralysis to the right in one case. The internal recti muscles were weak in two. There was limited elevation in one case and divergent strabismus in two cases.

The vision was not recorded in seven hospital cases. The vision in three eyes was not recorded in Table 1, because the poor vision could be explained by other than pathologic processes of the optic nerve, one eye being excessively myopic, and the other two revealing *retinitis proliferans*. The poorest recorded vision in the series was 3/60 in the right eye and 1/60 in the left eye, of a woman, aged thirty-one years.

The prognosis for the preservation of vision in cases of multiple sclerosis is good, but it is just the opposite in cases of tabetic atrophy. The prognosis is particularly good in cases of acute retrobulbar neuritis in which a considerable degree of the vision may return, and even become normal. In the long-standing cases of loss of vision the chances for the return of useful vision are poorer, but even in such cases loss of vision progressing to complete blindness, as with tabes, is rare.

Acute optic neuritis or retrobulbar neuritis which is rapid in development and improvement, and which occurs in young adults who have previously been healthy, should immediately suggest multiple sclerosis, especially if the process is unilateral and without signs of syphilis or intoxication.

#### SUMMARY

In multiple sclerosis, changes in the optic nerve are often early objective signs of the disease. About 50 per cent of the cases show changes in the disc, the most frequent change observed being a generalized pallor of the disc without loss of nerve substance. Simple optic atrophy, definite temporal pallor, and questionable temporal pallor are infrequent findings, each occurring in about the same proportion of cases. Disproportionality between the appearance of the fundus and the central and peripheral visual acuity is characteristic of multiple sclerosis. The generalized pallor of the discs may confuse this condition with tabetic atrophy, and the cases with acute retrobulbar neuritis present the same picture as those with toxic neuritis due to alcohol, tobacco, and accessory sinus disease.

## CLINICAL DIFFERENTIATION OF CASES WITH ABNORMAL X-RAY SHADOWS IN THE MEDIASTINUM

FRED W. GAARDE

The number of diseases which may cause x-ray shadows in the mediastinum are many, and therefore an abnormal x-ray finding is only a working basis from which the clinician must proceed to make a differential diagnosis by various methods. In order to determine the frequency of occurrence of symptoms of mediastinal disease detected by x-ray and the methods of making a correct clinical diagnosis in such cases, I reviewed the case records of all patients seen at the Mayo Clinic from 1918 to 1922, with abnormal x-ray findings in the mediastinum. A total of 158 cases was found. Cases of enlarged thymus in infants and children, and cases of intrathoracic goiter are not included. A classification of the diagnoses in the 158 cases is given in Table 1.

TABLE 1

### DIAGNOSES IN 158 CASES WITH ABNORMAL FINDINGS IN THE MEDIASTINUM

Aneurysm	67	Tuberculous glands	4
Hodgkin's disease	30	Lymphatic leukemia	4
Lymphosarcoma	26	Syphilitic mediastinitis	2
Carcinoma	13	Secondary sarcoma	2
Abscess		Pott's disease	2
Mediastinal	2	Enlarged thymus (adult)	1
Encapsulated empyema and lung abscess	4	Benign tumors (lipoma)	1

### SYMPTOMS RESULTING FROM PRESSURE

The accepted fact that signs and symptoms of affections of the mediastinum are in the main due to pressure exerted on near-by and contained structures is demonstrated in this series.

of cases. The more common symptoms from such pressure and the frequency with which they were encountered in the four predominating lesions is shown in Tables 2 and 3.

TABLE 2  
SYMPTOMS RESULTING FROM PRESSURE

Great vessels	Dilatation, superficial veins of upper extremities (one or both), head and neck, swelling of neck and face, cyanosis, unequal pulse volume, dyspnea, hydrothorax
Esophagus	Persistent dysphagia
Trachea and main bronchi	Stridor, dyspnea, cough, unequal saturation of right and left lungs
Nerve trunks Cardiac plexus Pleura	Pain
Sympathetic nerve	Unequal, contracted or dilated pupils, unilateral flushing or sweating
Recurrent laryngeal nerve	Hoarseness, cough, dyspnea, transient dysphagia

TABLE 3  
FREQUENCY OF OCCURRENCE OF SYMPTOMS

Lesion	Cases.	Great vessels.	Esophagus	Trachea and main bronchi	Dyspnea	Pain	Sympathetic nerve	Recurrent laryngeal nerve	No pressure
Aneurysm	67	14 (return flow)	8	4	35	37	13	21	9
Hodgkin's disease	30	10	2	6	11	6	2	5	16
Lymphosarcoma	26	10	2	4	10	4	2	1	8
Carcinoma	13	2	1	2	2	2	0	2	8

Hydrothorax from obstruction to the pulmonary and azygos veins was found in ten cases, and chylothorax in one patient.

with lymphosarcoma in which the thoracic duct was in some way involved. Pressure symptoms were also noted in some instances of the less predominant lesions listed in Table 1.

In thirty of the sixty-seven solid tumors, there were no pressure symptoms, or only those of a slight cough. In some instances, the severity of the symptoms was not indicative of the size of the tumor, one of the largest tumors in the series causing practically no symptoms. On the other hand, I recall a case in which the roentgenogram was negative, in which death was apparently due to tracheal pressure, and in which necropsy revealed a very small carcinoma, so situated as to cause almost complete obstruction to respiration. It is apparent from Table 2 that the character of pressure symptoms does not usually aid in differential diagnosis except that pain and involvement of the recurrent laryngeal and sympathetic nerves are more common in cases of aneurysm.

#### ANEURYSM

Aneurysm usually offers little difficulty in diagnosis, but occasionally presents a clinical picture sufficiently confusing to warrant mention of its distinguishing features. Development and progress is usually slower than in cases of solid tumors, and it is not uncommon to have a three, four, or five-year history previous to examination. Careful examination should be made for other signs of syphilis, and a history of a primary lesion elicited if possible. As seen in Table 3, pressure on the sympathetic and recurrent laryngeal nerves, and pain more often accompany aneurysm than other lesions. Tracheal tug, diastolic shock, murmur or bruit, and unequal pulse should suggest aneurysm. All mediastinal shadows should be fluoroscoped as a routine to detect expansile pulsation, and the latter must not be confused with transmitted pulsation, which is sometimes seen when a solid tumor impinges on the aorta. The absence of pulsation does not rule out aneurysm, as frequently a clot or organized thrombus will prevent perceptible expansion of the dilated vessel. The Wassermann test was positive in thirty-three of the sixty-seven patients. Aneurysm may sometimes be

ruled out of fluoroscopic examination when a normal aorta is seen through the shadow in question

#### HODGKIN'S DISEASE AND LYMPHOSARCOMA

These diseases will be considered together because of their similarity. Particular attention was given to details in the histories presented, in an effort to learn whether or not they re-



Fig. 199.—Hodgkin's disease. The shadow is usually bilateral

vealed anything of value in distinguishing these two diseases. Of the thirty cases of Hodgkin's disease, x-ray examination revealed the tumor to be bilateral in twenty-five, and unilateral in five, while in the twenty-six diagnosed lymphosarcomas, only ten were bilateral and sixteen were unilateral. In other words, 80 per cent of mediastinal shadows in Hodgkin's disease cast a vertical rectangular shadow centrally placed, while well over

half of the lymphosarcomas revealed a single rounded shadow with a clean-cut margin, and extending into one side of the thorax only (Figs 199, 200) This difference is not sufficient to serve as an absolute differential point, but seems worthy of consideration The age of the patient was of no value in differentiation, over 60 per cent of both lesions occurring between the ages of twenty and forty As to onset and rapidity of de

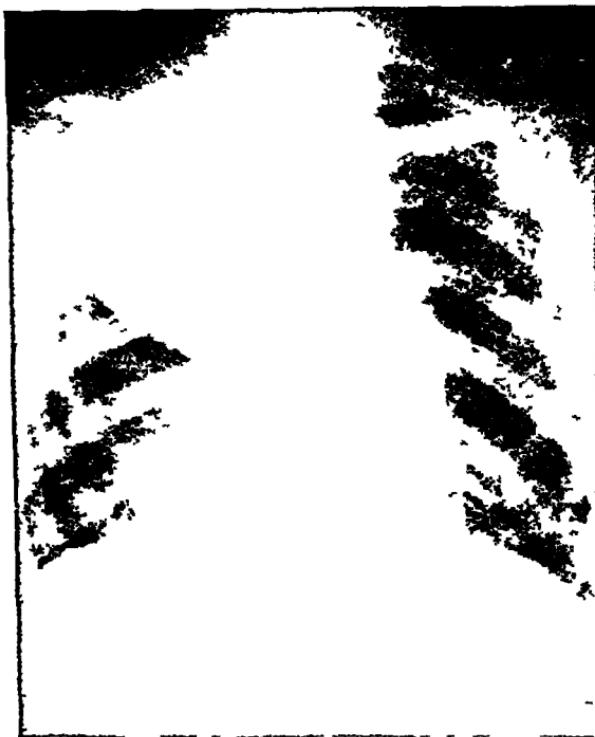


Fig 200.—Lymphosarcoma, showing unilateral lesion

velopment, lymphosarcoma might be regarded as the more vicious of the two Eight patients with Hodgkin's disease had had glandular enlargement for two years previous to examination, while all those with lymphosarcoma, except those who had had treatment, gave a history of glandular enlargement not exceeding a year However, there was a sufficient number of patients with acute Hodgkin's disease to prohibit the onset and

rate of development being considered as distinguishing features. Itching of the skin was present in eight, or approximately 26 per cent of the cases of Hodgkin's disease, only two patients with lymphosarcoma had a similar complaint. Lemon found itching of the skin present in 20 per cent of his series, and regarded the symptom as sufficiently important to suggest Hodgkin's disease, if associated with glandular enlargement.

The positive distinction between lymphosarcoma and Hodgkin's disease lies in microscopic examination of a gland, and even here, pathologists occasionally fail to agree. In Hodgkin's disease, usually the diseased glands were widely distributed, they were found in the cervical region in practically all cases, and in the supraclavicular and axillary regions in approximately half of the thirty cases. This is in contrast to mediastinal lymphosarcoma, in which only the glands in the supraclavicular region were usually diseased. In a few instances, however, cervical glands and other lymph nodes were involved. Of the fifty-six lymphomas included in this series, it was possible to obtain a gland for diagnosis in forty-seven.

It is often difficult to palpate supraclavicular glands. When they are deeply situated, it is sometimes necessary to have the patient assume varied positions, such as flexion of the neck, dropping the shoulder, and thereby lowering the clavicle in order that they may be palpated.

#### CARCINOMA

Carcinoma is usually secondary to growths elsewhere. In this series of thirteen cases, two were apparently primary, probably having their origin in the epithelium of the bronchi, trachea, or esophagus. Eleven were secondary to disease elsewhere: the breast in six, the cervix in two, the uterus in one, and the esophagus in two. Carcinoma has a greater tendency to invade the surrounding tissues, and is likely to appear in the roentgenogram as a unilateral infiltrating lesion (Fig. 201). Two exceptions were found, in which the x-ray revealed a smooth thickening of the mediastinum, and a definite diagnosis of carcinoma was made by examination of a supraclavicular

gland. That we do not see more secondary lesions from the esophagus is due to the fact that death ensues before extensive metastasis has had time to take place. Necropsy reveals metastatic mediastinal glands in a large proportion of cases.

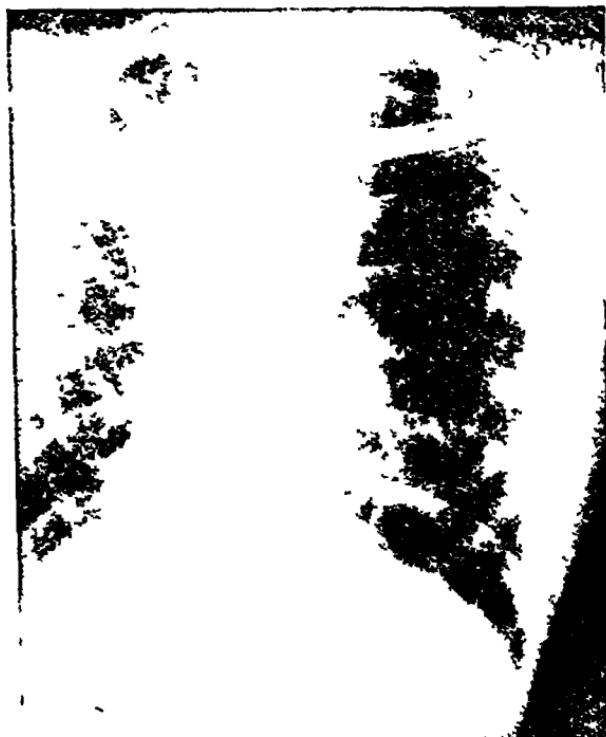


Fig 201.—Carcinoma, secondary to carcinoma of the breast

in which they were not sufficiently enlarged to cast a shadow in the roentgenogram.

#### ABSCESS

Of the eight patients suffering with abscess, all had a definite history of inflammation, such as respiratory infection followed by persistent fever and leukocytosis of varying degree, and the usual evidences of pyogenic infection. It is most important to recognize this group because of the cure which may be offered by surgical means. Exploratory puncture for pus is



Fig 203.—Encapsulated empyema which resembles tumor



Fig 202.—Encapsulated empyema. Note similarity to lymphosarcoma (Fig 200)

warranted only after the careful exclusion of other lesions, especially aneurysms (Figs 202-204)



Fig. 204.—Same as Figure 203, after operation and recovery of patient

#### TUBERCULOUS GLANDS

There were four patients with tuberculous glands of the mediastinum. The x-ray shadows were uniformly bilateral, and in each case cervical glands of an inflammatory character had been present for two years or more. Removal of a cervical gland afforded a means of diagnosis in three cases, while in the fourth this procedure was considered unnecessary because of the presence of a discharging sinus of long standing. In the last case, the patient also had active pulmonary tuberculosis.

Two cases of inflammatory mediastinal glands which pointed in the suprasternal notch were observed. One case was definitely tuberculous, and broke down to sinus formation. The nature of the second lesion, which remained as a hard inflammatory mass for several months was obscure. The last com-

munication from this patient asserted that the mediastinal shadow had completely disappeared

#### LYMPHATIC LEUKEMIA

It is interesting to note that in the series of cases reviewed, lymphatic leukemia was as frequent an invader of the mediastinum as was tuberculosis, there being four cases of each. The  $\nu$ -ray shadows in the former were bilateral (Fig. 205), and di-



Fig. 205.—Lymphatic leukemia

agnosis was apparent by differential blood count. One patient had marked pressure symptoms

#### SYPHILITIC MEDIASTINITIS

Giffin has pointed out that it is important to be on the alert for cases of syphilitic mediastinitis, as this lesion is amenable

to treatment. He reports five cases in which the Wassermann reaction was positive. There were definite signs of pressure in all, such as cough, dyspnea or pain, and in two there was vascular obstruction. Four patients improved following treatment for syphilis, the fifth refusing to remain for observation. The two patients in the present survey had positive Wassermann reactions, and responded favorably to treatment. The diagnosis of syphilitic mediastinitis should not be considered proved unless the patient improves and the x-ray shadow disappears or is definitely reduced following treatment for syphilis. The two cases of sarcoma were both secondary to previously proved sarcomas of the testicles, hence the diagnosis was apparent.

#### POTT'S DISEASE

Abscess of Pott's disease was found to be responsible for two mediastinal shadows in the series. In each case the diagnosis was simple because of typical symptoms of tuberculosis of the vertebræ. This condition should be borne in mind in all abnormal x-ray findings, and the characteristic symptoms of the disease are not always present.

#### ENLARGED THYMUS

The case of enlarged thymus in an adult deserves special mention. The patient was twenty-four years of age, and had had vascular obstruction in the mediastinum, including stridor, cyanosis, and dyspnea for four months. No glands were available for biopsy, and a tentative diagnosis of lymphosarcoma was made, as this seemed the most probable lesion. The patient died suddenly the day after registration, and necropsy revealed an enormous thymus gland. Microscopic study failed to show any evidence of malignancy, and it is difficult to understand why the gland should produce symptoms of obstruction, and cause death within a period of four months.

#### BENIGN TUMORS

Aside from the single case of mediastinal lipoma which is reported in detail by Lemon in this volume, no benign tumors

were encountered in this series. Two dermoid cysts have been reported previously, the clew to the diagnosis in each case being the coughing up of hair. Although these tumors are classified histologically as benign, they are clinically malignant because of their anatomic position, usually proving fatal. This is demonstrable by Lemon's case of lipoma.

#### SUMMARY

Accurate differential diagnosis of diseases of the mediastinum is most important, as it is in some instances the means of effecting a cure or at least of prolonging life.  $\alpha$ -Ray treatment of lymphoma and leukemia may add months or years to the patient's life, and treatment for syphilis, and surgery for inflammatory lesions may afford complete cure in such cases.

The more important procedures which were followed routinely in making a differential diagnosis clinically, in 158 cases in which  $\alpha$ -ray examination indicated the presence of mediastinal disease are (1) fluoroscopy for expansile pulsation, (2) careful search for glands elsewhere, that a biopsy may give information with regard to the nature of the original tumor, (3) a painstaking history, especially to elicit the possibility of inflammation or syphilis, (4) Wassermann test, (5) leukocyte and differential count to rule out leukemia and inflammatory conditions, (6) exploratory puncture, which should not be done as a routine, caution being exercised lest an aneurysm be punctured (puncture has a definite place, however, and often leads to a diagnosis), and (7) careful physical examination for signs of intrathoracic pressure.

Although this general scheme may be followed, it is often extremely difficult to ascertain the exact nature of the disease. It is sometimes necessary to observe the patient for weeks, for example, while awaiting results from antisyphilitic or  $\alpha$ -ray treatment. Search for enlarged glands should also be made from time to time. The  $\tau$ -ray picture may reveal characteristics of certain tumors. Sometimes we may exhaust all the means at our disposal and still be unable to differentiate accurately until necropsy.

## LIPOMA OF THE MEDIASTINUM

WILLIS S. LEMON

The case reported here is, so far as I can ascertain, the first case of lipoma of the mediastinum to be correctly diagnosed during the life of the patient except by surgical exploration of the chest wall. The patient has recently died, and the diagnosis, which was made two years ago, was verified at necropsy. I will, therefore, review the procedures which led to the correct diagnosis.

The patient, a man aged forty-six years, came to the Clinic July 10, 1922. One of his brothers had died from pulmonary tuberculosis at the age of thirty-eight years. His father had died from peritonitis at the age of forty-four years, and his mother from carcinoma of the stomach at the age of sixty-seven years. One brother died from typhoid fever, three other brothers are living and in good health. The patient was married when he was twenty-seven, and has had seven children. His wife is in good health, and has never had a miscarriage, a significant fact when linked with a personal history entirely free from any venereal taint. The presence of tuberculosis in the family history, and the absence of syphilis in the personal history are significant, as these two diseases must always be borne in mind by the clinician in making a diagnostic survey.

The patient said that, on the whole, he had been healthy. He had had diphtheria and scarlet fever as a child, typhoid fever when twenty, and influenza during the epidemic of 1921. He had had a hemorrhoidectomy, and a right orchidectomy. The latter was the result of pain and swelling of the right testicle subsequent to traumatism a year before. The pathologist reported that the tissue was non-malignant. Had this report been different, a distinct relationship would have been established between the testicular lesion and the present thoracic disease.

It is well to remember that the testicle is descended out of the body cavity, but that metastasis from malignant processes within it takes place in the region of its origin, and affects the juxta-aortic glands, from which the disease may spread upward and involve the thoracic lymph nodes.

The patient came for examination mainly because of two complaints, dyspnea of five years' duration, and swelling or tumor of the left supraclavicular fossa of eighteen months' duration. He said that the dyspnea was only troublesome on exertion, and was not progressing. He had been in active work up to the time of his examination here, the degree of dyspnea only slightly interfering with his duties as a minister. He had consulted his physician eighteen months before coming to the Clinic, at the time when he first noticed the enlargement of the neck. The tumor seemed to be more nearly in the middle line of the neck, it was considered to be an enlargement of the thyroid and was so treated. Apparent improvement followed, both in the size of the tumor and the degree of dyspnea. Since that time, the tumor had apparently moved from its central position to the left, until it occupied a large part of the left supraclavicular fossa.

Four days before coming to the Mayo Clinic, the patient had a severe paroxysm of coughing, followed by a hemorrhage of a cupful of bright red blood. This was the only appearance of blood, cough had not been a disturbing symptom at any time. There had been no fever, no loss of weight or of strength, no anorexia and no pruritis. The general health was excellent, and body functions normal.

After taking the history the symptoms were considered. It is not necessary to attempt a discussion of all the conditions in which dyspnea is a predominant feature. Only those conditions that can be of long standing, and are compatible with vigorous health bear on this case. At the Mayo Clinic, patients with long standing, but not severe, dyspnea, usually suffer from one of the following conditions: (1) cardiac disease, (2) phthisis, (3) chronic bronchitis and emphysema, (4) chronic nephritis, (5) pulmonary fibrosis-pneumonokoniosis, (6) asthma,

and (7) space-occupying masses within the thorax (tumors, aneurysm, pericardial effusions, and tumors or effusions within the abdomen causing elevation of the diaphragm)

The term "dyspnea" is applied to many types and degrees of shortness of breath, from that experienced by the obese, to the severe, non-expansile type in cases in which the lung is impermeable to air, so that the chest is elevated, but the lung does not expand. Non-expansile dyspnea is seen in cases of acute pneumothorax, in those of emphysema when the lung is already in a state of inspiration and distended to its capacity, in cases of pleural effusions, adhesions, or in pulmonary fibrosis which is comparable to, and usually associated with, emphysema.

TABLE 1

CLASSIFICATION OF SYMPTOMS COMMON TO INCREASED PRESSURE

*Compression of veins*

Superior vena cava	Cyanosis, lividity of face Suffusion of conjunctiva Prominence and staring of eyes. Edema of face and neck, upper thorax and arms Distention and dilatation of superficial veins of face, neck, and upper part of body, including mammary and superior epigastric veins. Headache, vertigo, epistaxis, tinnitus, deafness, visual disturbances, somnolence
Vena azygos major	Dilated intercostal veins, especially right-sided Right hydrothorax Pericardial effusion
Inferior vena cava	Edema of lower body and legs Albuminuria-ascites-hepatic congestion Dilated superficial vessels of lower part of body
Right pulmonary veins	Hydrothorax and lung collapse

*Compression of arteries*

Aorta and its branches	Inequality of pulse, especially subclavian Alteration of pulsation in carotids Engorgement of left side of heart. Pallor, giddiness, and anginal pains.
Pulmonary artery	Cyanosis Engorgement of right side of heart Cardiac decompensation

*Compression of air passages*

Trachea	Stridor, dyspnea, usually inspiratory cough, suffocation
	Hemoptysis, bronchorrhea
Bronchi	Cough
	Faulty aeration of portion of lungs with resulting findings common to atelectasis

*Compression of tubes and ducts*

Esophagus	Dysphagia, transient, if due to pressure of nerves
Thoracic duct	Emaciation, chylothorax, chyluria incites

*Compression of heart and pericardium*

	Displacement downward
	Effusion
	Irregular heart action arrhythmia
	Non-expansile pulsation

*Compression of nerves*

Vagus	Irregular heart action, slowing, syncope Vomiting, dysphagia, coughing, often simulating whooping cough or asthma
Inferior laryngeal	Paralysis of post crico arytenoid muscle with stridor, gander cough, dyspnea
Sympathetic	Irregular pupils, dilated with irritation, contracted with paralysis Flushing of face, pallor, unilateral sweating
Phrenic nerves	Unilateral paralysis of diaphragm Shoulder pain Hiccup
Intercostal	Neuralgia along course of nerves

*Compression of sternum and spine*

Sternum	Bulging, substernal pain, girdle sensation Erosion
Spine	Erosion of vertebrae sensory and motor disturbances below level Paraplegia

Inspiratory dyspnea with obstruction causes an overexpansion of the upper chest and a recession of the lower. It is usually urgent and of short duration. Whether the obstruction is due to an intrabronchial or an extrabronchial lesion, the more nearly it is placed to the larynx, the more probable is its association with stridor. This is an important consideration, es-

pecially in the localization of tumors of various character that may produce other signs of bronchostenosis. Inspiratory dyspnea without obstruction simply hurries thoracic movements, and may be of varying intensity. Expiratory dyspnea is pathognomonic of asthma, and of the asthmatic manifestations of emphysema, especially when combined with chronic bronchitis.

The patient's dyspnea, which was of the inspiratory type without evidence of obstruction, was never urgent and might have been due to any of the diseases mentioned, except asthma. The facts obtained during physical examination, and discussed later, were necessary to place responsibility for this symptom.

The significance of hemoptysis in a given case always merits careful consideration. Cabot quotes statistics from the German army that place in order of frequency the following causes of hemoptysis among soldiers: tuberculosis, trauma, pneumonia, heart disease, bronchiectasis, influenza, syphilis, abscess and gangrene of the lung, hydatid cysts, and irritating fumes. In his own experience, in civil practice, the order of frequency is as follows: tuberculosis, mitral disease (unspecified causes), pulmonary thrombosis or embolism, pulmonary abscess or gangrene, bronchiectasis, pneumonia, aneurysm, trauma, and neoplasm. This list is more nearly in keeping with my own experience. In chronic conditions such as mediastinal lipoma, one may expect the following diseases to be responsible for hemoptysis: tuberculosis, heart disease (mitral endocarditis), from unspecified causes, chronic suppurative pulmonary disease, including abscess and bronchiectasis, pneumonokoniosis, neoplasm and aneurysm. It is evident from these lists, and from more complete ones by French, that tuberculosis is the most important factor in producing hemoptysis. In view of the family history of this patient, the suddenness of the onset of hemorrhage, and the history of long-continued although moderate dyspnea, the examination will necessarily be directed toward the end of proving with certainty whether or not tuberculosis alone could be the explanation. It is equally important, however, to note that the usual accompaniments of tubercular activity are wanting, the patient's fundamental functions are

undisturbed, his weight, strength, and temperature are normal, his nervous system is unaffected, and he has so little cough and sputum that they were not mentioned by him as symptoms. These are the weak points in the suggestion that tuberculosis might be responsible for his illness.

During the last eighteen months, a tumor had developed, and occupied the supraclavicular fossa. Such a tumor is always important, because in that location it usually indicates the existence of malignancy below the diaphragm.

*Physical examination*—The patient was a large man, although not obese, he weighed 221 pounds, his normal weight, and was six feet tall. A soft, elastic semifluctuant tumor, about 5 cm in diameter, lay in the left supraclavicular fossa, and in the right were what appeared to be hard and enlarged lymph nodes, only one of which, however, seemed of great consequence. Mediastinal dulness was increased to the right, and the heart appeared to be displaced toward the left. Bronchophony was heard over this area of increased dulness, but there was no suggestion of a bulging of the chest wall, no expansile pulsation, and no evidence of diastolic shock on palpation. D'Espine's sign was marked. Another important negative sign was the lack of congestion and cyanosis of the neck and face, when the patient assumed a stooping posture. Very distant breath sounds were heard over the whole right side of the chest, with diminished respiratory excursion on that side. The expiratory sounds heard over the right chest, posteriorly, were harsh and prolonged, and unaccompanied by adventitious sounds. There was a well marked network of enlarged veins at the line of attachment of the diaphragm. Examination of other parts of the body failed to reveal evidence of disease.

The urinalysis was normal, also the blood count, in both differential count and numbers of leukocytes, and the hemoglobin percentage and number of erythrocytes were well within normal limits. The Wassermann reaction was negative. This confirmed the original opinion that syphilis could not properly be considered a factor. Examination of the nose, throat, and larynx failed to reveal diagnostic evidence. With clinical findings

so suggestive as those in this case, an examination of the larynx is especially valuable to determine the integrity of the two recurrent laryngeal nerves. X-ray examination of the chest revealed a large, lobulated mediastinal tumor, extending into the right side, this suggested the possibility of a lymphosarcoma. The esophagus was displaced toward the left.

Having determined that the fundamental cause is a mediastinal tumor, the next step is to determine its character. This tumor could not be inflammatory, because of the paucity of symptoms, their long continuance, and the absence of laboratory confirmation. Table 1 is a brief outline of the symptoms which may arise from a tumor in this region. It represents my own experience with more than 100 mediastinal tumors, and the experience of others, as reported in the literature. The symptoms are, of course, numerous, because of the many important structures that pass through the narrow confines of the mediastinum, bounded as it is on two surfaces by unyielding bony walls. Laterally, there is more space available, and consequently tumors not directly confined to the middle line are less prone to produce symptoms. What actually happens has been clearly shown by Gaarde (p 1236). Two facts stand out namely, the amount of pressure needed before symptoms appear, and the paucity of symptoms in many cases of large tumors, a fact noted by Doyle and myself when studying Hodgkin's disease.

In the effort to determine the nature of this tumor, we have recourse to a surgical procedure which will often yield diagnostic evidence when the lungs and mediastinum are involved. The lymph node in the right supraclavicular fossa is the common site of metastatic involvement from these organs, and therefore a biopsy report is essential. Accordingly, July 13, 1922, what appeared to be a lymph node was removed from the right supraclavicular fossa. This was reported by the pathologist to be osteochondrolipoma. July 17, the tumor from the left supraclavicular fossa was removed, and was found to be a simple lipoma. Neither of these tumors seemed to be connected, by digitations or otherwise, with the tissues of the mediastinum. Thus, the removal of supraclavicular nodes was disappointing.

in that they did not reveal the exact character of the intrathoracic tumor. However, this evidence became valuable when associated with the facts that, although not really obese, the patient weighed 221 pounds, that his complaint was of longer standing than is usual in cases of mediastinal tumor, and that he had two benign tumors, both lipomatous in structure. Inasmuch as it is known that lipoma becomes lobulated, the opinion that the large lobulated mediastinal mass was benign and a lipoma was strengthened. Accordingly, a diagnosis of lipoma of the mediastinum was made, and the patient treated by radiotherapy, and allowed to return to his home. This was two years ago. As time passed, more serious manifestations of pressure appeared. The patient's physician reported that compression of the veins became manifest with distinct cyanosis of the lips during seizures of paroxysmal coughing, although no evidence of Stokes' collar appeared. The veins on the upper part of the body and the epigastrium became distinctly dilated, and headache, occasional vertigo, and a decided somnolence developed. The right lung, which previously had given evidence only of bronchostenosis, became more and more collapsed, although no effusion was found at any time. Later the dyspnea gave place to marked air hunger, and the patient was very cyanotic. The dyspnea was evidently both inspiratory and expiratory, and the breath sounds were associated with asthmatic adventitious sounds. Only slight hemoptysis recurred, but there was a decided bronchorrhea, evidently an irritation resulting from pressure on the bronchi. During the last few months of illness, the patient had intermittent attacks of very violent coughing, lasting for one to many hours, yet the left lung remained well aerated. The right lung was poorly aerated at all times.

Death occurred in January, 1924. Necropsy was performed and I quote from Dr. Leach's letter: "The tumor of the mediastinum at the time of necropsy was larger than a quart cup, firmly adherent to the trachea, aorta and bronchi of the right lung. It had expanded into the right chest cavity, compressing the right lung to the extent that little air could pass into the lung. The tumor was removed and sections sent to laboratories. Reports confirmed the clinical diagnosis of a lipoma."

## DISCUSSION

I shall not attempt to review the literature, but am appending as complete a bibliography as I have been able to compile. The cases of lipoma described by Fitz, Kronlein, Cruveilhier, Ewing, and Leopold are perhaps the most interesting in the literature.

Reginald H. Fitz' report, in which he shows the route by which lipomas may reach the intrapleural space, deserves special mention. These lipomas develop from the subpleural fat or from the subperitoneal fat, forcing upward through the diaphragm. Other cases are mentioned, which show that the fatty digitations may proceed downward from the neck into the thoracic cavity, or may originate from the fat within the mediastinum itself. The case under consideration seems to belong to the latter group. That such tumors may point outwardly seems authenticated, and may explain the fact that fatty tumors as well as those of other character may lie both without and within the chest, connected by a narrowed isthmus of tissue proceeding through the thoracic wall.

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## SYMPTOMS AND DIAGNOSIS OF NONTUBERCULOUS PULMONARY SUPPURATION

H MILTON CONNER

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Under "nontuberculous pulmonary suppuration" I shall include all nontuberculous diseases in which the chief symptoms are cough and the expectoration of purulent sputum (1) pulmonary abscess and gangrene, (2) bronchiectasis, including putrid bronchitis or fetid bronchitis, (3) nontuberculous infection of the lung (Hamman and Wolman, and others), and (4) mycotic infections of the lung (actinomycosis, blastomycosis, sporotrichosis, coccidioidal granuloma, and aspergillosis). Since empyema results in excessive expectoration only when there is rupture into a bronchus, the condition will not be included.

### PULMONARY ABSCESS AND GANGRENE

The etiologic and pathologic features of these two conditions may well be discussed together, because the line of distinction is very vague, and because they usually cannot be separated symptomatically, not even at necropsy. The essential difference seems to be the predominance of putrefactive organisms in gangrene. The chief determining factor appears to be that patients with poor general resistance seem more likely to develop gangrene. The chief differential features of gangrene, clinically, are the almost indescribable fetor of the sputum and breath, and the extreme and usually fatal illness.

Formerly, abscess seemed to follow lobar pneumonia in the greater number of cases, but recently the postoperative abscess, especially that following tonsillectomy under ether, seems the most common in some clinics. Whittemore found that 61 per cent of eighty-six cases at the Massachusetts General Hospital

followed operations under general anesthesia, while 40 per cent followed tonsillectomy. In his series, bronchopneumonia was a frequent precursor, thirteen of his cases having this origin while only two followed lobar pneumonia. Lemon, in a report of eighty-one cases from the Mayo Clinic, gives as causes pneumonia in thirty-one cases, colds, grippe, pleurisy, typhoid,

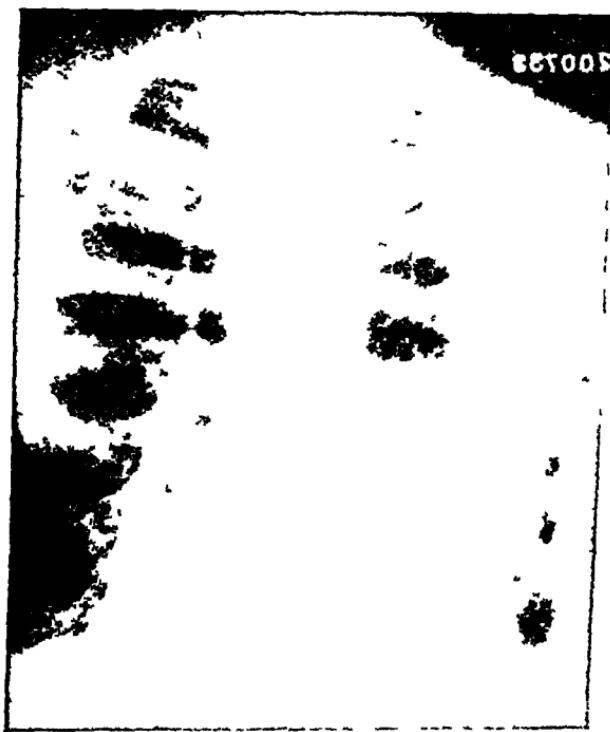


Fig. 206.—Abscess of the right lower lobe. Note cavity represented by area of decreased density.

measles, and scarlet fever in nineteen, operations, especially extraction of teeth, and tonsillectomy, performed elsewhere, under general anesthesia in seventeen, trauma in two, and unknown in twelve. Wessler, in 100 cases, found twenty-one following tonsillectomy, five following other operations, and thirty-seven following pneumonia. Twenty-one were of insidious origin (colds, grippe, and so forth), and fifteen were due to vari-

ous other causes. One of the cases in the Mayo Clinic developed ten years after the entrance of a piece of wood into the lung by injury of the chest wall. At operation, the splinter measuring about 2.5 by 0.5 cm. was found in the abscess.

Various organisms are found, streptococci, pneumococci, fusiform bacilli, and spirilla, being the most common.



Fig. 207.—Abscess of the right upper lobe. Note cavity immediately below clavicle, and straight line representing interlobar pleura.

In considering the various series of cases, it is found that in general, abscesses of the lower lobe (Fig. 206) are twice as common as of the upper (Fig. 207), except those following operation under general anesthesia, when the reverse is true. Abscesses are also approximately twice as common on the right side as on the left. Lemon gives the following locations: Upper lobe fifteen cases; lower lobe forty-five cases; middle lobe eight cases.

He summarized Walter's, Wessler's, Norris and Landis', and his own series, and found a total of eighty-six cases in the upper lobe, 192 in the lower lobe, and fourteen in the middle lobe. Wessler gives the location as follows. Aspiration abscess, upper lobe eighteen, lower lobe nine, and middle lobe one, nonaspiration abscess, upper lobe twenty-four, lower lobe forty-four, and middle lobe three. In Whittemore's series, forty-three abscesses were in the upper lobe, and twenty-nine in the lower. If of embolic origin, the abscesses are almost always multiple, and are scattered in various areas in both lungs.\*

Aschner has shown that abscesses following operation under general anesthesia usually are, in reality, bronchiectatic abscesses. In any cases in which respiratory tract symptoms follow operation, especially tonsillectomy under general anesthesia, a developing abscess should be suspected even though symptoms and signs, and x-ray examination point to bronchopneumonia. So far as can be determined, abscess of the lung has followed tonsillectomy under local anesthesia only once at the Mayo Clinic during a period in which more than 20,000 tonsillectomies were performed.

The cases following pneumonia, colds, grippe, and so forth, are more difficult to diagnose. The persistence of cough, fever, and expectoration after the normal time for the subsidence of the pneumonia should at once excite suspicion of abscess or empyema, since almost all cases of so-called unresolved pneumonia eventually prove to be one or the other of these. Cough and expectoration developing in the course of septicemia, middle ear disease, endocarditis, and so forth, should excite suspicion of embolic abscess of the lung. Cough is always present, and one of the chief symptoms. In the postoperative cases, it usually begins a few days after operation, and gradually

\* Since it is now quite generally conceded that abscesses following operation under a general anesthetic are due to aspiration of infected material during narcosis, one would expect them to be most common in the lower lobes, since the tendency would be to aspirate in the line of the main air current, which is downward. Whittemore explains the greater incidence in the upper lobe as a result of the cough which follows aspiration, forcing the material into the bronchus leading to the upper lobe.

increases Wessler has found that the fetid expectoration almost invariably begins thirteen or fourteen days after the operation, but my experience does not entirely coincide with his. At first the cough is nonproductive. Purulent sputum gradually increases in amount and often becomes fetid. Usually a large amount is expectorated suddenly, after a violent coughing spell when something seems to break. As much as a pint of purulent, often very foul, sometimes sweet material, may be coughed up at one time. The sputum then decreases in amount. Recovery may occur, or the same syndrome may recur. Often a considerable amount of sputum is expectorated daily for months or years. The sputum may be blood-tinged or a frank hemorrhage may occur. Tuberculosis bacilli are absent, and elastic tissue fibers are often found, especially if the abscess is recent. However, my experience is that elastic fibers are found in only about half the cases, Whittemore finds them in one-third.

Pain often is not present, but occasionally may be severe on account of the accompanying pleurisy. There usually is tenderness over the affected area if it extends to the pleura. Fever generally is high and intermittent in type until rupture occurs, and much lower afterward. There usually is slight fever, especially in the afternoon, even in the chronic cases. Chills and sweats, especially before rupture of the abscess, general failure, anorexia, loss of strength and weight, and anemia of varying degree are often present. In the acute stage the patient generally is very sick, while in the chronic stage he usually does not have the good general health ordinarily found in cases of bronchiectasis.

In general the physical signs will depend on the location and stage of the process. In the acute case the patient looks very ill, often is dyspneic, has a rapid respiration, sweating, hectic flush, and diminished expansion of the affected side. In the chronic stage the clubbed fingers are the most obvious sign. There is diminished expansion of the affected side, marked if fibrosis is extensive. The fibrosis may also result in displacement of the heart toward the diseased side. Often the trachea is similarly displaced, and in marked fibrosis a scoliosis results.

with the convexity toward the sound side. In the stage of consolidation the signs on palpation are indistinguishable from those of bronchopneumonia with its increased fremitus. If a cavity is present after rupture the fremitus is likely to be increased, while if the cavity is full of sputum the fremitus may be much reduced. If the bronchus is plugged, the fremitus will be absent. Diminished expansion of the affected side is also shown by palpation. Lemon says "I have always insisted on the value of palpation with the finger-tip between the ribs as a localizing measure in cases in which it is difficult or impossible to find the abscess by  $\tau$ -ray or physical examination. In cases in which the abscess is demonstrated by  $\tau$ -ray, the area mapped out by finger palpation corresponds almost exactly."

In the stage of consolidation there may be impaired resonance or dulness on percussion, while if there is a large empty cavity, there may be tympany or cracked-pot resonance. If the cavity is full, percussion may yield the same findings as in the stage of consolidation. In the stage of consolidation the auscultatory signs will be those of a bronchopneumonia with its bronchial breathing, increased vocal resonance and whispered voice. Moist rales may be present. If the bronchus is plugged, there will be diminished vocal resonance, and lessened or absent breath sounds. If a cavity is empty and of sufficient size, there may be amphoric or cavernous breathing and consonating rales. In the "silent" cases the patient should always be asked to cough. The expectoration of sputum will often bring out true signs of a cavity. The  $\tau$ -ray is one of the most valuable means of diagnosis. Often, however, the picture will be indistinguishable from that of pneumonia, localized empyema, bronchiectasis, or occasionally from a malignancy of the lung or pleura. The typical picture is that of a cavity, with or without a fluid level surrounded by an area of consolidation. Leukocytosis is usually present at any stage. Anemia of varying grade exists.

The main diagnostic points in cases of abscess of the lung are the sudden expectoration of purulent material by a patient acutely ill following an operation, especially of the tonsils under general anesthesia or following pneumonia, the clubbed fingers,

leukocytosis, elastic tissue in the sputum, and the x-ray findings. The condition must be distinguished from bronchiectasis, ruptured empyema, tuberculosis, malignancy of the lung or pleura, bronchopneumonia, nontuberculous infection of the lung, actinomycosis, blastomycosis, sporotrichosis, coccidioidal granuloma, aspergillosis, and abscess of neighboring organs or pericardial empyema ruptured into the lung, or ruptured infected dermoid cyst (clinically an abscess).

Bronchiectasis may be distinguished by its longer history, gradual onset, slight illness, little or no fever, greater tendency to be confined to the bases and to be bilateral, more diffuse distribution, little or absent leukocytosis, absence of elastic tissue, and the x-ray picture.

Empyema ruptured into a bronchus differs in the greater pain, former signs of fluid, evidences of thickened pleura, usual absence of elastic tissue, and the x-ray findings. Encapsulated empyema ruptured into a bronchus may be distinguished by the greater pain, if the condition is not interlobar, the location of the lesion, peripherally, mediastinally, or between the lung and diaphragm, or in one of the interlobar fissures; the usual absence of elastic tissue in the sputum, and the x-ray findings. If the empyema is interlobar, the x-ray signs may be indistinguishable except by the location of the lesion in one of the fissures. Even then it may be only a good guess (Fig. 208).

Tuberculosis may be differentiated by the longer illness before profuse expectoration began, the tendency to be bilateral in almost all cases, with profuse expectoration, the greater tendency to location in the upper half of the lungs, the x-ray findings, and, most important, the presence of the tuberculosis bacillus in the sputum. In one case I found great difficulty in diagnosis since there was no preceding pneumonia or operation. The lesion was located in the upper lobe, the signs of a cavity were typical, and there were frequent very large hemorrhages, necessitating transfusion. The absence of tuberculosis bacilli in many specimens of sputum, the acute onset, and the recovery of the patient, made the diagnosis of abscess seem warranted.

Malignancy of the lung or pleura rarely leads to the expec-

toration of large quantities of pus unless there is a softening and breaking down, or pressure on a bronchus, producing bronchiectasis. Under these conditions differentiation may be difficult, the detection of pieces of the tumor in the sputum or the so-called malignant cells in the pleural fluid, and also the bloody pleural fluid are the best distinguishing features. Of course, metastasis



Fig. 203.—Abscess of the right lung, probably in the middle lobe. Note wedge shape, suggesting that the abscess had its origin in encapsulated empyema.

in the supraclavicular region points to malignancy. If an abscess develops insidiously in an aged person one should always suspect malignancy with necrosis.

Nontuberculous infection of the lung or so called chronic pneumonia of the lower lobe, is distinguished by its longer history, smaller amount of sputum, lack of sudden expectora-

tion, absence of elastic tissue in the sputum, the good general health of the patient, and the roentgenogram

Pulmonary actinomycosis, blastomycosis, sporotrichosis, aspergillosis and coccidioidal granuloma, or California disease, are distinguished mainly by the discovery of the causative organism in the sputum. I have seen good pathologists mistake coccidi-



Fig. 209.—Dermoid cyst in the left mediastinum, simulating lung abscess. Note fluid level and air bubble (Love).

oidal granuloma for tuberculosis until the coccidioides was found in the sections. These closely resemble the blastomycoses.

The possibility of a ruptured infected dermoid cyst must be kept in mind. This may be distinguished by the location near the mediastinum, the more circular appearance, and the coughing up of hair. One case in the Clinic was mistaken for a simple abscess until operation disclosed abundant hair in the

cavity. In this case the picture of abscess was perfect, including the roentgenogram and clubbed fingers (Fig 209). If dermoid cyst had been suspected the diagnosis could have been made, since the patient remembered after the operation that once he had coughed up a long hair.

#### BRONCHIECTASIS

Bronchiectasis may follow almost any disease which produces chronic inflammation of the bronchi, chronic cough, and fibrosis.



Fig 210.—Bronchiectasis of the lower half of both lungs

of the lung or pleura. The mechanism of its production is much in dispute, but practically all observers are agreed that the three conditions mentioned are almost always causative factors. The greater number seem to follow acute bronchitis, which becomes chronic, and influenza. Elliott, in a review of

forty cases, found one-half due to bronchitis, seven to pleurisy, seven to pneumonia, and three to influenza

Various organisms are found, especially the streptococcus, pneumococcus, and most of all, the influenza bacillus. Certain observers feel that the influenza bacillus is almost always responsible. In some cases fusiform bacilli and spirilla, resembling and probably identical with those of Vincent, have been found



Fig. 211.—Bronchiectasis of the right base

Also, a monilia has been obtained by culture in many cases, but Lemon, who has been much interested in this work, is inclined to believe that it is a secondary invader

Bronchiectasis is bilateral in about half the cases and is usually in the lower lobe (Fig. 210). The upper lobe may be involved. Four of the five cases in the upper lobe, reported by McRae and Funk, were accompanied by, and probably due to tuberculosis

The dilatation may be saccular (Fig. 211), cylindrical or fusiform, and the size varies from a few millimeters to 3 cm or more.

Cough is the principal symptom, and combined with expectoration is the *sine qua non* of the diagnosis. It is usually loose, in fact, a so-called loose cough should at once excite suspicion of bronchiectasis. It begins rather insidiously after influenza or pneumonia, or may be a continuation of the cough that has accompanied these diseases, or an acute cold. It gradually increases in intensity, and is most likely to be present when the patient changes position, as in going to bed, arising in the morning, stooping, and so forth, at which time a large amount of sputum is raised.

Expectoration is at first small in amount, but gradually increases, until enormous amounts are expectorated. A pint in twenty-four hours is not at all unusual, some patients expectorating much more, and others, much less. Large amounts are usually expectorated in a short time until the cavity is emptied, when the coughing ceases. Often at examination a very large amount may be obtained by having the patient lie over the examining table with the head much lower than the hips. In this position only a little coughing will empty the cavity of a large amount of sputum. It is purulent, usually rather thin, runs easily, is yellowish or greenish and often of a very foul odor. Many of these patients are social outcasts because of this fetor. One of my patients had a milky white sputum which contained an excessive amount of fat. This could best be explained on the assumption that the inflammation had extended through the pleura into the mediastinum, and that a small fistula of the thoracic duct had been established. It may have been due to the breaking down of leukocytes, being chylous rather than chymous in character.

The general health usually remains good for many years, although sooner or later patients often succumb to such conditions as bronchopneumonia, brain abscess and amyloid disease, resulting directly or indirectly from the bronchiectasis. Fever may occur intermittently, but there may be weeks or months of freedom from it. It is usually mild unless broncho-

pneumonia has developed, as often happens. Chills and sweats are uncommon. Anemia may be present, but is mild. Usually there is little loss of weight and strength. Dyspnea, often asthmatic in character, is present to some extent in nearly all well-developed cases. Pain in the chest may occur if the condition extends to the pleura. Vomiting may occur on account of the fetor. In the very prolonged cases a gradual deterioration with partial cardiac failure may develop.

Clubbed fingers, and often clubbed toes, may appear within a surprisingly short time after the onset of symptoms, and sometimes clubbing of the extremity of the nose. Occasionally there is no clubbing. If there is considerable fibrosis, there will be diminished expansion of the affected side, possibly also a displaced heart, and considerable evidence of emphysema, such as barrel-shaped chest.

Palpation does not yield much information unless there are large cavities, or marked fibrosis, in such cases, the fremitus will be increased.

Percussion will usually disclose dulness if the cavities are full, and may disclose varying degrees of resonance if the cavities are empty, and tympany if the cavities are very large and empty. If the lesion is deep-seated, there may be very little change.

Auscultation, if the cavities are full, may show only suppressed breath sounds and a varying number of coarse and fine moist râles especially with cough, and often sibilant and sonorous râles. If the cavities are empty, there may be amphoric breathing, bronchophony, whispering pectoriloquy, the so-called veiled puff, and a varying number of moist râles, especially the so-called consonating râles. If the process is deep, there may be almost no auscultatory signs. If diffuse, scattered moist and dry râles may be the only physical finding. The x-ray often shows the dilated bronchi very clearly (Fig. 211), especially in the stereoscopic plate, but in some cases, nothing more than an infiltration is shown. One should always examine the chest before and after emptying, to bring out these variations, and x-ray examination, at first non-diagnostic, may become diagnostic if repeated when cavities are emptied.

The sputum is persistently negative for tuberculosis bacilli, except in cases associated with tuberculosis

The main diagnostic points are the chronic paroxysmal cough, usually of years' duration, profuse, often foul expectoration, clubbed fingers, and comparatively good general health

Bronchiectasis must be differentiated from abscess of the lung,\* ruptured empyema, tuberculosis, bronchopneumonia, nontuberculous infection of the lung, actinomycosis, blastomycosis, sporotrichosis, aspergillosis, and coccidioidal granuloma of the lung, malignancy of the lung or pleura, subphrenic, hepatic, perinephritic or mediastinal abscess, Pott's abscess of the spine, or empyema of the pericardium or infected dermoid cyst ruptured into the lung and bronchus

Ruptured empyema is distinguished by the usual symptoms of pleurisy, more acute onset, more severe illness, sudden excessive expectoration, leukocytosis, fever, former signs of fluid, present signs of thickened pleura, and often of pneumothorax or pyopneumothorax and the x-ray findings. Ruptured localized empyema differs in its location at the periphery, mediastinally, between the lung and diaphragm, or in the line of the interlobar fissures, as shown by the x-ray or physical findings, the greater amount of pain unless the condition is interlobar, the sudden rupture, leukocytosis, fever and greater illness

Tuberculosis is characterized by a more severe illness, predominance of signs in the upper lobes, a tendency to be bilateral in almost all cases in which expectoration is excessive, the presence of tuberculosis bacilli in the sputum, and usually the absence of clubbed fingers

It must be emphasized that bronchiectasis is one of the common causes of profuse hemorrhage, and also that marked clubbing of the fingers is seldom found in cases of tuberculosis unless bronchiectasis accompanied it

In nontuberculous infection of the lung, or chronic pneumonia, there is less sputum, lack of fetor, less tendency to clubbed fingers, and the tendency to recurrence rather than continuation of the condition. The same may be said of the other conditions

\* The differentiation from abscess of the lung was considered under the discussion of that disease

outlined in the discussion of their differentiation from abscess of the lung

There are cases in which the clinical history is not characteristic, the physical findings not clear-cut, and the x-ray picture doubtful. In these cases, abscess, bronchiectasis and empyema cannot be distinguished, and may coexist. Chronic empyema, with or without fistula, tends to create fibrosis, and this with the resulting cough, may bring on bronchiectasis, also in the process of spontaneous cure of abscess, fibrosis may result which, with the cough and the infection of the bronchial walls, tends to form bronchiectasis. The reverse is also true with bronchiectasis there are prone to be exacerbations, the parenchyma may be infected and abscess develop, or the pleura becoming affected, empyema may result. In fact, the pleura is almost always somewhat affected.

#### NONTUBERCULOUS INFECTION OF THE LUNG

I shall discuss only briefly nontuberculous infection of the lung, which has been discussed previously by Hamman and Wolzman, Garvin, Lyal and Morita, Field, and myself. In 1921 I reported twenty-eight cases. Since then I have observed many more cases, but I have not changed the views expressed then.

The chief points in the diagnosis of nontuberculous infection of the lung are (1) cough for a prolonged period, either constant or with exacerbations, (2) little depreciation of general health, (3) little, if any, fever, and if present, intermittent, (4) lack of progression of the disease, (5) the lesion usually located in the base of the lung, and (6) absence of bacilli of tuberculosis in the sputum.

Nontuberculous infection of the lungs may be distinguished from tuberculous infection mainly by the location of the lesion in the base, by the less marked or absent depreciation in health, by lack of progression, and by the absence of bacilli of tuberculosis. Often there is leukocytosis. In at least nine of ten cases of tuberculosis, the infection is found in the upper lobes or apices, while almost the reverse is true of these cases. Recently Rosenblatt reported that, in 1,000 cases of tuberculosis, only three were primarily in the base of the lung. Seventeen of

eighteen patients with basilar lesions, admitted to the Bedford Hill Sanitarium with the diagnosis of tuberculosis, were found to be nontuberculous. In this connection, it is well to remember the dictum of Brown that "abnormal physical signs at one apex should be considered as due to pulmonary tuberculosis until proved not to be, while those at the base should be looked upon as not tuberculous until definitely proved tuberculous."

Nontuberculous infection of the lungs is differentiated from simple chronic bronchitis by the fact that chronic bronchitis is usually generalized, is often secondary to cardiac or other disease, has less tendency to the production of purulent sputum, usually does not cause exacerbation of symptoms, with temperature and usually does not produce leukocytosis. Moreover, in simple bronchitis, the râles are predominantly dry, whereas in this condition they are predominantly moist.

Bronchiectasis may be distinguished from nontuberculous infection of the lungs by clubbed fingers, and the more abundant foul sputum brought up by paroxysms of cough. Cough and expectoration are usually markedly affected by changes of position, such as lying and stooping. The cough in bronchiectasis is typically loose and a copious amount of the sputum may be produced by inversion. The sputum, if allowed to stand, often separates into three layers. There may be no leukocytosis in cases of bronchiectasis.

Bronchopneumonia is usually bilateral, acute, and not recurrent, whereas nontuberculous infection is chronic often unilateral, and recurrent. With bronchopneumonia there are signs of consolidation, while in nontuberculous infection such evidence is usually absent.

#### MYCOTIC INFECTIONS OF THE LUNG

The mycotic infections of the lung, actinomycosis, blastomycosis, sporotrichosis, aspergillosis, and coccidioidal granuloma cannot be discussed at length, but it should be emphasized that in any pulmonary suppuration, their occurrence must be thought of, and ruled out by examination of the sputum for the specific organism.

## MILIARY CALCIFICATION IN THE LUNG

CHARLES G. SUTHERLAND

From 1916 to 1920 approximately 60 000 roentgenographic examinations of the chest were made in the Mayo Clinic. About 30,000 of these revealed positive findings. I reviewed these plates recently and from them selected thirty-eight, the findings in which justified their inclusion in the category of metastasis of calcium as it has been described in the literature. This low incidence of 0.0616 per cent in the chest is in agreement with the findings of pathologists. The literature contains data concerning the experimental and pathologic aspects of the condition, but I found no reference to roentgenologic studies. As none of the patients included in this series died while at the Clinic, necropsy data are not available.

The lesions seen in the roentgenogram were multiple, miliary, calcified spots, varying in size from a pin point to two or three microns, they were round, discrete and sharp in outline, were distributed through both lung fields, seldom were seen above the first interspace, and generally were more numerous toward the base. In number they varied from eight to ten large spots to a shower of innumerable miliary particles.

In our series there were twenty-four (64.86 per cent) males, and thirteen (35.14 per cent) females, the average age of the males was forty-four years, and of the females forty-eight. Two of the males had passed the second decade of life, six the third, eight the fourth, six the fifth, and two the sixth, of the females three had passed the third decade, five the fourth, three the fifth, one the sixth, and one the seventh. The majority were from rural districts. Twelve were from Iowa, five from Illinois, three from Indiana, two each from Minnesota, Missouri, South Dakota and Kansas, and one each from North Dakota, Nebraska,

Michigan, Arizona, Colorado, Wyoming, Wisconsin, Ontario, and Saskatchewan

In only one of the cases (Case 1, Fig. 212) the roentgen findings suggested involvement of the lung equal to that in the two cases in which the pathologic findings were described by Harbitz

*Case 1*—A woman, aged fifty-one years, came to the Clinic in March, 1918, complaining of heart trouble and goiter. Her general health had been poor for eleven years. She had had hysterectomy at forty-one for fibromas



Fig. 212.—Miliary calcification of the lung, showing a perfect shower of rounded, sharply demarcated, opaque areas, no history of bone destruction, but pathologic lesions of gastro intestinal tract and thyroid.

of the uterus. Goiter had been noticeable for twenty years, irritability had commenced five years before, and loss of weight and strength one and one half years later. The growth of the goiter had been more rapid in the last six months. There was a history of gastric pain two hours after eating relieved by food and by soda, frequent hunger pains at night, sour vomitus

with traces of blood, and traces of blood in the stool, intermittently over a period of eleven years. Three years before, attacks of pain had come on in the upper abdomen, radiating to the right shoulder, with vomiting, belching and local soreness. Jaundice developed. All of the patient's upper teeth had been removed, in the lower teeth there were marked dental caries and pyorhea. April 3, 1918, the metabolic rate was +53. The left superior thyroid was divided and ligated April 6, and the vessels were found to be very small. April 15, a thyroidectomy was performed and the pathologic report



Fig. 213.—Miliary calcification in the lung, less profuse than Figure 212. Note the absence of involvement above the first interspace

was "multiple degenerating colloid and fetal adenoma, with very slight hypertrophy the weight of the gland was 80 gm." April 25, 1918, the metabolic rate was +11. Five days later, laparotomy was performed, the surgical findings were "subacute, perforating duodenal ulcer, chronic appendicitis, and chronic catarrhal cholecystitis (strawberry gallbladder)." Following this, the metabolic rate reached +25, and there was a gain in weight of 8.5 pounds. A clinical diagnosis of myocardial degeneration and fibrillation was made at this time. Constipation more severe in the last three or four years was present. A letter from the patient two years after opera-

tion, stated that her general health was much improved, but that she had marked shortness of breath and less than half her normal strength.

Nineteen other roentgenograms were characteristic of this lesion, but the miliary calcifications were less numerous (Case 4, Fig. 213), than they were in Case 1. The calcification in these nineteen was associated with a wide variety of lesions, in several it would be difficult to trace a connection between the clinical or surgical findings and the calcification. The nineteen cases are briefly summarized as follows:

**Case 2**—A man, aged thirty, had Raynaud's disease in the hands, rheumatic pains, tonsils 2, and pyorrhea. He had been in bed three weeks with left sided pneumonia two years previously.

**Case 3**—A woman, aged fifty five, had an inoperable carcinoma of the breast. A tumor had been removed six years before. She also had long-standing pyorrhea.

**Case 4**—A man, aged forty six, had had indefinite stomach trouble for six or seven years. Physical examination was negative.

**Case 5**—A man, aged thirty-four, had had osteomyelitis of the right humerus for six weeks. He had sustained a fracture of the hip ten years before, which united without incident.

**Case 6**—A man, aged forty-five with a duodenal ulcer, had had gastric symptoms for fifteen years. He had pyorrhea and dental caries, had sustained a fracture of the neck of the femur with apparent nonunion eighteen months before examination, and had a Charcot hip.

**Case 7**—A man, aged sixty-one, had had aortic stenosis, mitral insufficiency, and decompensation for one year. He also had marked oral sepsis.

**Case 8**—A man, aged forty five, had had osteomyelitis of the rib for ten months, also marked oral sepsis.

**Case 9**—A man, aged forty two, had emptied a jar of cement two years before examination, and two weeks later commenced to cough, expectorating small blood stained "particles of cement." Clinically the chest was negative. Operation was performed for epithelioma of the lip.

**Case 10**—A woman, aged forty nine, had had intermittent attacks of indefinite stomach trouble for thirty years. She was once free from this complaint for five or six years. She was operated on, and cholecystitis with multiple stones, and multiple duodenal ulcers were found.

**Case 11**—A man, aged forty six, had had erythema nodosum for six months. He had dental caries and pyorrhea. A tonsillectomy had been performed two years before.

**Case 12**—A man, aged sixty, had had marked oral sepsis, tonsillitis, and angiocarcinoma of the soft tissues of the arm.

**Case 13**—A man, aged thirty seven, was weak, and had lost strength. Physical examination was negative.

**Case 14** — A man, aged fifty, had symptoms suggestive of myocardial degeneration

**Case 15** — A man, aged forty-six, had infected hydronephrosis on the left side, practically all the renal substance was destroyed

**Case 16** — A woman, aged forty-seven, had adenoma of the thyroid, the enlargement was slight. She also had convulsions from unknown cause

**Case 17** — A man, aged forty-four, was examined, and the findings were negative

**Case 18** — A man, aged fifty-one, had had asthmatic attacks for four years, lasting from one to three weeks. He also had dental caries, and slight tonsillitis. There were no tuberculosis bacilli in the sputum. He had had pleurisy twenty-five years before

**Case 19** — A man, aged thirty, had had a tumor of the left testicle, said to be sarcoma, removed seven months before. There was metastasis to the abdomen and chest. Constipation had been marked

**Case 20** — A man, aged forty-eight, had epithelioma of the right side of the larynx

In eighteen other plates there were a few widely scattered miliary calcifications (Case 21, Fig 214) which we have designated the "phlebolith type" on account of their similarity in numbers and distribution to the phleboliths so frequently seen in the pelvic vessels in roentgenograms made of the kidney, ureter and bladder areas. These were associated with a wide variety of lesions in other parts of the body, and presented the same difficulty of correlation as the preceding series

**Case 21** — A woman, aged sixty-two, had had carcinoma of the cecum and ascending colon for eighteen months, and chronic diarrhea for three months

**Case 22** — A woman, aged fifty-eight, had multiple adenoma of the thyroid of forty-four years' duration

**Case 23** — A woman, aged thirty-eight, had multiple, hemorrhagic, fibrous and calcareous, degenerating adenoma in a colloid goiter, also multiple fibromyomas, and chronic cystic oophoritis

**Case 24** — A coal miner, aged thirty-three, had had tonsillitis five years before. Constipation was rather marked. He had had attacks of stomach trouble eleven, seven, and two years before

**Case 25** — A woman, aged forty-four, had marked cholecystitis, with stones in the gallbladder cystic and common ducts. She had had jaundice eleven years before operation and again seven months before. The tonsils were moderately enlarged

**Case 26** — A man aged fifty-four, had syphilis for one year. He also had syphilitic in advanced grade

**Case 27** — A man, aged fifty-six, appeared clinically to have primary carcinoma of the liver. He had had chills for one year and night sweats

about every ten days. He had lost strength, and had been constipated for years. There was severe oral sepsis, and the tonsils were slightly septic.

**Case 28** —A woman, aged fifty-six, had duodenal ulcer revealed by the x-ray. She had had chronic arthritis of the hands fifteen years before. Tonsillectomy had been performed, and small tonsils found.

**Case 29** —A woman, aged forty-four, had moderate pyorrhea. She had also had rheumatism in the shoulders and neck every winter for the last four or five years.

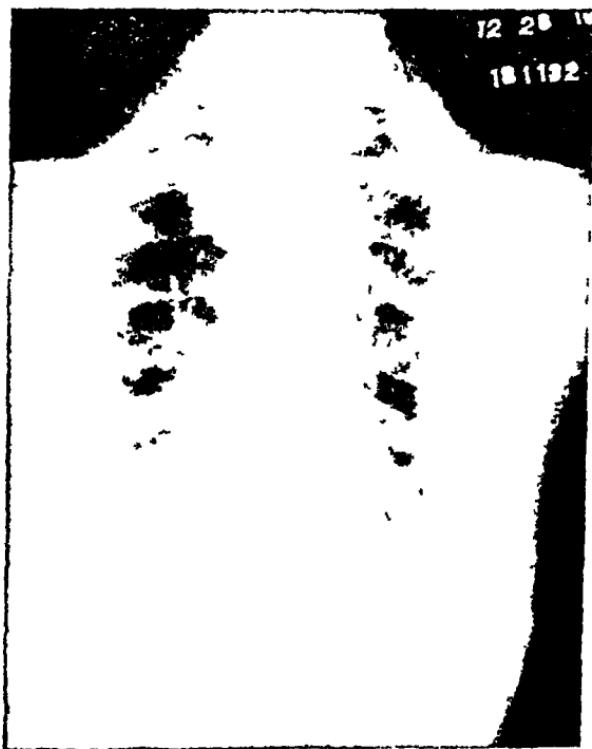


Fig. 214.—Miliary calcification in the lung, "phlebolith type" very similar in appearance to the phleboliths seen in kidney, ureter, bladder rays

**Case 30** —A man, aged fifty-five, had squamous-cell epithelioma of the left cheek (operative finding), pyorrhea, and had had pneumonia eleven years before.

**Case 31** —A man, aged thirty-seven, had had a tumor of the bladder for two years.

**Case 32** —A man, aged twenty-five, had moderately enlarged tonsils and a right inguinal bubonocele.

**Case 33** —A man, aged fifty-four, had recurrent carcinoma of the cecum, and dental caries.

Case 34—A woman, aged thirty-two, had chronic catarrhal cholecystitis (early strawberry gallbladder), with several stones in the gallbladder. The pancreas was lobulated and there was marked hepatitis of the liver. Numerous adhesions were found around the appendix at operation, which contained a number of concretions.

Case 35—A man, aged twenty-six, had old gonorrhreal arthritis of the right hip with ankylosis.

Case 36—A woman, aged seventy, had frequent attacks of tonsillitis. Seven years before she had mild rheumatic fever for one year.

Case 37—A woman, aged forty-three, had bilateral ethmoiditis, sinusitis, and multiple combined pleurisy.

Case 38—A woman, aged thirty-four, had had tonsillectomy four years before, and severe influenza sixteen months before. Chronic pleuritis with adhesions was evident at examination.

#### DISCUSSION

In considering these cases, the question arises whether or not the diseases known to exist were adequate cause of the metastasis. The majority of the patients had some lesion which theoretically could have been an important etiologic factor. The patients with malignancy, tuberculosis, and syphilis were all susceptible to lesions of bone even though such lesions were not demonstrated. However, in the cases in this series, in which there were definite lesions of bone, the lesions were of a type and duration that made sufficient solution of calcium to cause the secondary lesion improbable, in the majority of instances. The fact that an overwhelming number of patients having gastric disorders, circulatory disturbances, lesions of the kidney, alterations of the thyroid and other internal secretions, and impairment of the excretory functions did not develop calcium metastasis, makes me doubtful of this hypothesis with regard to the latter. The fact that the majority of the patients came from rural districts, in which the calcium content of the water was known to be high, suggested a cause, but again, there were large numbers from the same districts with similar lesions who did not show any evidence of calcium metastasis. There is little doubt that many of these primary lesions and to some extent the habitat, are factors in the oversaturation of the blood with calcium salts, but to this must be added some metabolic anomaly causing a disbalance that favors the precipi-

tation of the calcium salts from the blood. It is questionable whether the term "metastasis" is appropriate in cases in which there is no evidence that the calcium has been absorbed from other tissues.

#### DIFFERENTIAL DIAGNOSIS

Two cases were observed in which very fine calcification, suggesting in places a powdering, with splotches of varying size (Fig. 215), running through the field, which the stereoscope



Fig. 215.—Calcification of the pleura associated with a hypernephroma of the kidney.

proved to be in the pleura. One case was associated with gastric trouble of fifteen years' duration, with findings at operation of chronic catarrhal appendicitis with obliteration of the mucosa, and with a history of three attacks of pneumonia. In the other case a hypernephroma of the kidney about 20 cm. in diameter,

and containing considerable calcareous material was found at operation

Calcifications of the pleura are commonly confined to one portion, and a pleuritic lesion is manifested by fibrosis, retraction and adhesions. The shadow is of lesser density and is more conglomerate



Fig 216.—Pneumoconiosis shadow softer, less distinct individual areas are irregular in outline

Calcification in the region of the hilum is encountered comparatively often in the routine examination of chest plates. The calcification is seldom discrete, but appears as conglomerate areas, varying in size and shape. In one series investigated, this condition seemed to be more common in patients whose tonsils were or had been diseased, or had been removed.

Pneumoconiosis (Fig 216) in the diffuse form gives a much

softer and more indistinct shadow than miliary calcification; as the condition advances, there is a tendency to the formation of conglomerate shadows, usually in the middle third of the lung field, and toward the periphery

Tuberculosis generally has associated evidence of a lesion of the lung tissue, the areas of calcification are irregular in shape, and vary greatly in size. The lesions are commonly in the upper half of the lung fields and the apices are generally involved.

#### SUMMARY

Miliary calcification of the lung is a distinct pathologic condition. The lesions are characteristic calcified spots, discrete, round, and having marked absorptive power for the roentgen rays. These spots are widely distributed throughout both lung fields, but are seldom seen above the anterior level of the first rib. They are generally more numerous toward the base. The lesions occur in apparently normal lung tissue, and the patients usually give no history of antecedent pulmonary disease.

The disorders with which the condition has been associated are of wide variety and in many cases it is difficult to trace any connection. Oversaturation of the blood with calcium salts seems to be a factor, associated with some not yet defined metabolic anomaly which causes a precipitation of these calcium salts from the blood.

Clinically there is no syndrome indicative of the anomaly, and for its discovery we are dependent on the roentgen ray. Admitting the rarity of the abnormality and its usual lack of symptoms or grave consequences, it is none the less interesting and deserves further study.

#### APPENDIX DISCUSSION OF THE LITERATURE

Virchow, in 1858, described calcareous infiltration of the lung, of the endocardium of the left ventricle, of the pulmonary veins, of the gastro-intestinal mucous membranes, and of the kidneys. He associated this process with diseases of bone, more particularly the primary or secondary bone tumors, in the course

of which calcium salts are set free. He noted it also in osteomalacia and in leukemic conditions.

That calcareous degeneration was preceded or accompanied by deposits of a soapy material was the conclusion of Klotz, in 1905, and further experimental work demonstrated, in his opinion, an intimate association between abnormal presence of fats and the presence of calcification. He thought that the endothelial cells of the capillaries of the lungs had the property of splitting fats and liberating fatty acid radicals.

Wells, in 1911, reviewed the subject of calcification and ossification, and published the results of original research by himself and his associates. Comparing normal ossification and pathologic calcification he pointed out many characteristics common to the two. Experimental work in other laboratories had demonstrated that it was possible to cause extensive and typical metastatic calcification by intraperitoneal injection of soluble calcium salts into rabbits. His own work suggested that the calcium salts exerted a specific influence on the connective-tissue cells, stimulating them to originate active growth, and to undergo metaplasia. The fact that the deposition of calcium was most common in the lungs, stomach and kidneys was significant, because in the tissues of these three organs the acids of the body are mainly excreted. It seemed reasonable to assume that the precipitation of the calcium in the condition of metastatic calcification occurred in these organs because calcium salts are slightly less soluble in the more alkaline fluids of their tissues. He found calcium to be held in solution in the blood in combinations and proportions entirely out of accord with aqueous solutions, and two possible agencies were suggested to account for this phenomenon, the colloids and the carbon dioxid. Under ordinary conditions, the precipitation of calcium was prevented by the colloids, no matter how completely the carbon dioxid was removed from the blood. But in extreme cases of oversaturation, the calcium was precipitated, especially in the lungs where carbon dioxid is given off, in the stomach and kidneys where it is neutralized by acid excretion, or in the arterial intima where the lymph, rich in carbon dioxid

and poor in colloid, gives up its carbon dioxide to the arterial blood

Wells, in 1915, in an article on "metastatic calcification" pointed out that, contrary to the rule in ordinary pathologic calcification, the deposit takes place in tissues not previously altered or injured, and in organs that are not often the seat of calcification, independent of local lesions. He asserted that metastatic calcification provides a striking demonstration of the important part played by the carbon dioxide of the blood and tissue fluids in the transportation, absorption and deposition of calcium salts.

Harbitz, in 1918, presented the pathologic findings in a woman with extensive calcification in the lungs. She had had acute rheumatism when a child, and again at the age of forty-five, several large hemorrhages from the stomach in the three years previous to death, occasional severe epistaxis, and increased menstrual flow. For ten years she had been subject to shortness of breath on exertion, and later dyspnea and cyanosis, and within the last year before death, she had had edema of the legs, and anasarca. The necropsy findings were as follows: absence of fluid in the pleural cavities, a few fibrous bands over the left lung, with general adhesions over the right lung. The lungs were six times their normal weight, stood without support when placed on their bases, did not float, were apparently full of small solid particles, and under the pleura were many small, white masses of mineral deposit. The substance of the lung could be cut only with difficulty, and it felt like porous bone. The cut surface was reddish brown, with numerous small holes in an extensive stroma, a bloody, frothy fluid exuded. Air was present throughout the lung, but the air-containing tissue was less in amount than the interstitial tissue with mineral deposits in it. There was no calcification of the pulmonary arteries, larger bronchi, trachea or larynx. Frozen sections of the lung revealed numerous round and oval concretions in the interstitial tissue with compression of the alveoli. Decalcified sections showed the concretions to be of a lamellar structure, concentric, but without needle-shaped crystals or larger masses, the clumps

were lying in the alveolar tissues and encroached on the alveolar spaces

The stroma was increased in amount, in places sclerotic, anthracotic, and infiltrated with round cells. The veins and capillaries in the septa were dilated, and there were hemorrhagic infiltrations into the septa and into the alveoli, and small bronchi, in places the alveoli appeared as narrow clefts, in others as small spaces with swollen desquamated cells, and in still others as large spaces, the lungs were not entirely solid anywhere. No signs of old, diffuse inflammatory processes, such as chronic bronchitis or pneumonia, could be found.

Harbitz reported a second case, that of a woman of sixty-five years, who died of intestinal obstruction and marasmus. Necropsy revealed a diffuse and extensive calcification of the lungs, and possibly of the stomach, associated with primary disease of the bones of the skull. The cranium was normal in form and thickness, but very soft, consisting mainly of diploe, on both of the surfaces were irregular, dark red and grayish spots. The exact nature of the disease of the bone was not determined. The lungs were large, grayish red, and looked as if they had been powdered, on removal they retained their form, were solid and heavy, but floated in water. The cut surface seemed as though dusted with fine sand, and a grayish-red, frothy fluid could be pressed out.

Reviewing the literature, he agreed that many of the causes of calcification might be looked on as metastatic in Virchow's sense, and advanced other theories such as interference with elimination by way of the kidney, stomach or intestine, thus diminishing calcium excretion, degeneration or dystrophic conditions in the lungs producing precipitation of the calcium salts, chronic stasis in the circulatory system and secondary nutritive changes in the walls of the alveoli, or a defect in one of the organs of internal secretion, particularly the parathyroids, the thyroids, thymus or hypophysis.

His conclusions were that calcification in apparently normal tissues, and especially in the lungs, must be due to a "constitutional anomaly" or metabolic disturbance of unknown

nature, connected with the low acidity of the blood as it gives up carbon dioxid

Crane reported two interesting cases of metastasis of calcium one associated with bone metastasis from carcinoma of the prostrate, the other, a case in which the Wassermann reaction was positive, and no lesions of the bone were actually elicited. He called attention to the fact that calcium deposition might occur in any necrotic tissue

## CHRONIC ANTERIOR POLIOMYELITIS WITH ACHONDROPLASIA: REPORT OF A CASE

MANDRED W COMFORT

Jansen, in 1921, advanced the hypothesis that achondroplasia results from abnormalities of the amnion, and grouped the symptoms into those of infolding, and those of dwarfism. Symptoms of infolding, including kyphosis of the base of the skull, sagittal narrowing of the foramen magnum, depression of the nasal bridge, reduction in size of the sella turcica, lumbodorsal kyphosis, and other abnormalities of the spine, are due to a smallness of the amnion, which causes a rolling up of the fetus on its long axis. Dwarf phenomena are manifested by a relative shortness of the extremities, shortness of the chest, and a deformed pelvis. This dwarfism is usually due to a smallness of the amnion with increased hydrostatic and direct pressure on the parts, in the milder forms, however, stunting may be due to the increased hydrostatic pressure of a hydramnion. In either case the increase in pressure causes an impoverished nutrition of the parts, chiefly of the bones laid down in cartilage, and a diminution of growth and the power of growth. Bullard and George have divided the cases into two groups roentgenologically. In those in which puberty is reached without much deformity, the shaft is shorter, its cortex near the middle is thickened, and the medulla decreased in width, while near the epiphyses the opposite obtains. There may be slight bowing. In children the diaphyses are cup-shaped at the epiphyseal ends, producing a T-shaped and uneven epiphyseal line. In the second group, there are secondary joint lesions, deformity, and a marked development of the foregoing changes. Pathologically, the most important process in the epiphysis is one of retardation of growth and ossification, while in the diaphysis

there is a production by the periosteum of relatively more bone, which is not completed by the addition of endochondral bone

Achondroplasia is uncommon, its combination with chronic anterior poliomyelitis is of sufficient rarity to justify placing this case on record

A woman, aged thirty-two years, entered the Clinic December 14, 1923. She had an only child who is said to be dwarved, resembling the patient at the same age. The patient is the sixth in a family of eight children. She was always undersized and small for her age; the rate of development did not equal that of her brothers and sisters, and at the age of twelve years growth apparently ceased. Normal menstruation began at the age of thirteen. Two pregnancies occurred, the first being a breech presentation, with delivery of a dead child. The second child was born five years ago, with delivery by cesarean section.

The present illness began in the spring of 1921, and was preceded by a severe attack of tonsillitis. The earliest symptoms were lack of endurance, weakness of the right hand, and a dull aching pain over the external surface of the right arm, which was felt daily at the onset. The pain gradually diminished until it was rarely felt, the weakness slowly increased, in six months slight difficulty was experienced in raising the arm above the head. It was not until one year before examination, however, that this movement became impossible. Later motion of this extremity diminished to practically nil.

In the spring of 1922, rapidly increasing weakness was first noted in the right leg. In walking, a limp was noticeable. By the summer of 1922, the gait was "waddling," walking being accomplished by throwing the weight on the hip and swinging the entire opposite side of the body forward. The patient began to stumble and fall. Flexion of the legs was weaker than extension. In climbing stairs, the foot could scarcely be elevated sufficiently to place it on the next step, but once placed there, the weight of the body could be raised with only a moderate amount of effort. The left leg also became affected very slightly. Fifty feet became the minimal possible distance for walking.

One year before examination, the left hand became weak, and later the shoulder, but fair motion still persists in this extremity. Within the last few months function of the left lower extremity has diminished to a point almost equal to the right, walking can be accomplished only with the greatest difficulty and slowness, and with assistance. When the patient is sitting, the smallest force tends to overbalance. Muscle twitchings have been felt since the onset of the trouble. Jerking movements of small amplitude have been observed in the fingers. Standing or grasping with the hand sets up a quivering of the muscles, overlying fat and skin of the thighs and the forearm.

Examination revealed a short and very obese female, 4 feet 3 inches in height, weighing 120 pounds. The limbs were short in comparison with the

length of the trunk, which was that of a normal adult, the proximal segments being slightly shorter proportionately than the distal. All the bones were present, and scarcely or not at all bent. The measurements were

	Cm.
Head maximal length, nasion to external occipital protuberance	17
Width, interparietal boss	16-
Circumference	56
Cephalic index	91
Base of skull to infragluteal fold	67
Infragluteal fold to sole of foot	47
Acromion to tip of middle finger	50
Humerus	20
Ulna	17
Fingers	6-7-7 5-7
Anterior superior iliac spine to line of knee-joint	33
Tibia	23
Fibula	36
Pelvic measurements	
Interspinous	20
Intercrest	25
Intertrochanteric	28
Exterior conjugate	18
Conjugate vera	7
(Arch somewhat narrow)	

The head was large and brachycephalic in type, the frontal and the parietal bosses were prominent, the face was broad, but the basal bridge was not noticeably depressed. The cranial nerves showed no abnormalities. The hair was of normal distribution and quantity. Adipose tissue, which was markedly developed over the abdomen and the thighs, was not painful on pressure.

The thorax was of good circumference, and the breasts were large and pendulous. The sternum showed a tendency to anterior rotation. The costal margin flared outward a bit, no trace of the rachitic rosary or Harrison groove could be found. The lumbar curve was accentuated, the dorsal region rounded, and the pelvis contracted.

The extremities showed no deformities except their shortness. The hands were short and broad, but were not typical trident hands. The deep reflexes were active, but weak, the abdominal reflexes could not be elicited no pathologic reflexes were obtained.

The musculature was generally and markedly involved, graded on a basis of 1 to 4, in the right upper extremity, strength, tonus, speed and amplitude of movement were reduced to —3 or 4, adduction of the thumb, flexion and extension of the digits, supination and pronation of forearms were fairly well preserved. The right lower extremity was affected almost equally, extension of the knee, adduction, abduction, internal and external rotation

of the hip being fairly well accomplished in a favorable position of the part. In the left upper extremity the loss of strength, tonus and speed were graded —3, amplitude of movement, however, was normal everywhere, except in the muscles of the shoulder girdle where a reduction to —3 degree was noted. The left lower extremity was least involved, its functional activity being impaired to —1 to 3, and the flexors affected more than the extensors. Range of motion was normal, except for the anterior group of leg muscles, which could effect but slight movement of the ankle and the toes. An atrophy



Fig. 217 (Case reported herewith) —Obesity, pseudohypertrophic appearance of the deltoids, wasting of the thenar and hypothenar eminences, drop feet, and relative shortness of the proximal segments of the extremities.

commensurate with the weakness was present, though obscured by the large accumulations of panniculus adiposus which in some locations simulated hypertrophy. Fibrillary twitchings were observed in all muscles where the fat did not obscure inspection. The almost helpless condition of the patient prevented tests for coöordination. Walking was possible only when the patient was led, this being accomplished by shifting the weight to one limb, then swinging the opposite half of the body forward. A twitching movement of the fingers was observed, and attributed to fibrillations of the interossei.

All forms of sensation were unimpaired, speech was unaffected. The patient could scarcely sit alone, and rolled over like a ball when overbalanced.

The systolic blood pressure was 104, the diastolic 80. The pulse rate varied from 70 to 110, the temperature from 98° to 99.8°, the respiration from 20 to 24. Examination of the urine was negative. There were 3,880,000 erythrocytes, 7,600 leukocytes, and the hemoglobin was 68 per cent. The blood Wassermann reaction was negative. The spinal fluid gave a negative

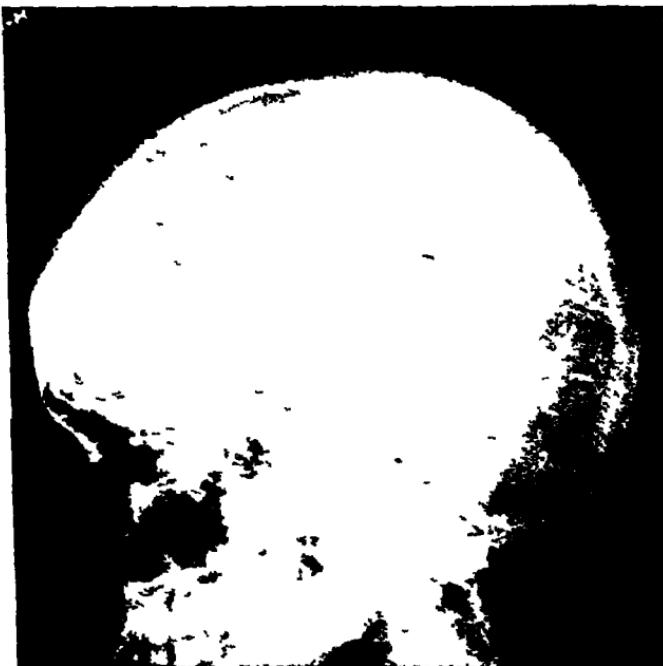


Fig. 218.—Same case. Roentgenogram showing the brachycephalic head and the kyphosis basis crani.

Wassermann and Nonne, and a normal pressure and cytosis. The basal metabolic rate was +5. Roentgenologic studies revealed a brachycephalic skull with a suggestion of a kyphosis of the base of the skull, thickening of the cortex and narrowing of the medulla near the middle of the long bones, the opposite condition obtaining near the epiphyses, and projection of the apex of the fibula into the line of the knee-joint (Figs. 217-220).

#### DISCUSSION

Chronic poliomyelitis is a chronic degeneration of the anterior horn cells, terminating in complete destruction. The origin of the bacteriologic or toxic agents concerned is usually



Fig. 219.—Same case. Roentgenogram showing the cortical and medullary changes, and the normal angle of the second and fifth metacarpal bones.

assumed to be foci of infection elsewhere. The history of tonsillitis immediately preceding the onset in the case reported here, and the infected tonsils permit the assumption that this view is probably correct. The history of the paralysis preceding the atrophy, the involvement of whole groups of muscles and even of a whole extremity, instead of individual muscles, and the fairly rapid course of the disease permits a clinical diagnosis of chronic poliomyelitis. However, it should be remembered that there exists in the minds of many observers no definite line of demarcation between this disease and progressive muscular atrophy. The latter is possibly an abiotrophic or degenerative process. The possibility of the coexistence of a disease of an

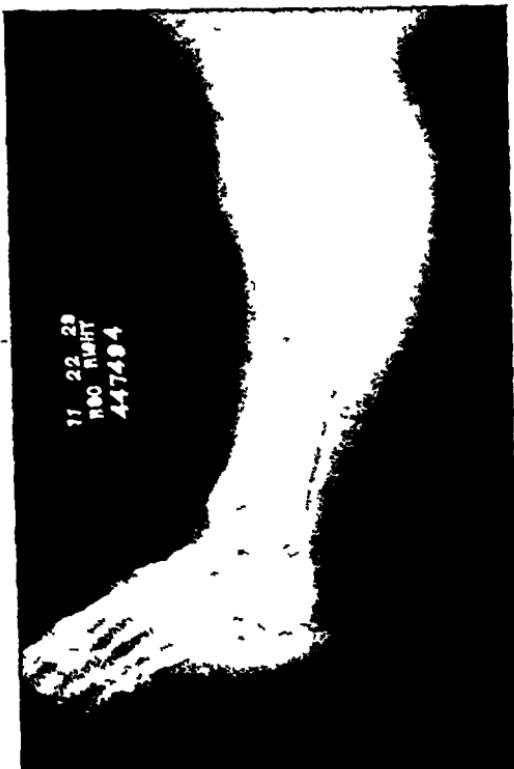


Fig 220.—Same case Roentgenogram showing the cortical thickening near the middle and thinning toward the epiphyseal ends the diameter of the medulli increased peripherally and diminished centrally, and the projection of the apex of the fibula into the line of the knee-joint

abiotrophic origin with one caused by an embryonically impaired power of growth suggests an interesting question. Can an abiotrophic tendency be produced not only by a hereditary weakness of the germ plasm designed to produce certain structures, but also in utero by mechanical factors, such as increased pressure and impaired nutrition, which impart a lowered vitality and resistance to continued function, and ultimately lead to premature death of the tissue? Certainly it is not a far cry from the embryonically impaired power of growth of achondroplasia to the early death and degeneration of progressive muscular atrophy.



# THE PROTEAN MANIFESTATIONS OF CHRONIC INFECTIOUS ARTHRITIS

(With a Note on Treatment)

PHILIP S HENCH

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The symptoms of chronic infectious arthritis in its milder and simpler forms are generally confined to muscles and joints. In its more severe, progressive forms, however, chronic infectious arthritis is quite protean in nature. It might be defined as a disease which is systemic in distribution, with its major manifestations in articular and periarticular structures, but with important manifestations which may be apparent in other structures and systems of the body. Secondary or associated phenomena arising as the result of the systemic infection and intoxication may be divided into two groups secondary infections in various parts of the body, and secondary metabolic changes in certain of its functions. In the severe forms of arthritis, therefore, the associated disturbances in other systems may so complicate the picture as to lead to difficulty in diagnosis. For example, an accompanying secondary anemia has at times been so profound as seriously to suggest the pernicious type. Marked loss of weight with anorexia, anemia, and gastric achlorhydria often bring up the suspicion of malignancy. Accompanying myocardial involvement may predominate in the clinical picture. An associated splenomegaly with progressive anemia has, on occasion, raised the issue as to the possibility of an accompanying splenic anemia of Banti's type, or of one of the other types of splenic anemia. A focal nephritis, or a definite deficiency in carbohydrate metabolism, may be a complication. Hyperthyroidism must be excluded in certain cases with tachycardia, loss of weight, sweating, and tremor of the extremities. Four cases of chronic infectious arthritis (chronic polyarthritis or arthritis

deformans) are presented to illustrate this diversity of the clinical pictures

#### REPORT OF CASES

**Case 1**—A man, aged thirty-four years, came to the Clinic because of rheumatism. His family history and past history had been negative. Fifteen years before examination the patient had begun to have pain and a swelling in the left knee. Later the left ankle, right knee, left shoulder, elbows and right ankle had become involved. Various treatments were tried, including osteopathy, naturopathy, electrical treatment, sulphur baths, and synovectomy, followed by baking and massage twice a week for two months, none afforded relief. The patient's diet had been low in protein and acid foods. Ten years before coming to the Clinic his weight was 150 pounds. He had lost weight, at first slowly, and later more rapidly, until when he came to the Clinic, his weight was 117 pounds. He had noted sweating of the hands and feet, which felt alternately cold and hot. His appetite was poor.

The blood pressure was 120 systolic, and 70 diastolic, the temperature normal, and the pulse rate 132. On repeated examinations, with rest, the pulse varied from 90 to 120. The joints showed marked hydrops of the knees, with marked proximal and distal muscular atrophy, and typical spindle formation. The condition of the fingers and arms was similar. There was general muscular weakness and a definite tremor of the extended hands. The skin, especially of the hands and feet, was moist. The von Graefe sign was absent, and the thyroid was apparently normal. The heart rate was accelerated. Examination for possible foci of infection revealed only one periapically infected tooth, the sinuses, gallbladder, appendix, and prostate were all negative, the tonsils had been cleanly removed, and there was no chronic constipation.

The Wassermann reaction was negative, the blood count and chemistry, renal functional tests, and gastric analysis were all normal. An electrocardiogram was negative except for increased rate. The preliminary diagnosis was chronic infectious arthritis, and possibly hyperthyroidism.

**Comment**—Hyperthyroidism was suspected on the first examination, on account of the tachycardia, loss of weight, sweating of the extremities, and tremor of the hands. The basal metabolic rate, however, was normal (+3 and +3). Such a clinical suspicion is raised fairly frequently. Loss of weight is common in marked arthritis, and with the muscular atrophy accounts for the weakness and tremor so commonly seen. The sweaty hands are one of the most characteristic signs of arthritis of the infectious type. Cold clammy hands, generally associated with a systolic blood pressure of about 110, or at least below the expected tension, constitute a strong

differential point between the infectious and the so-called metabolic or senescent type of arthritis, which comes on in later years as an exaggeration of the normal catabolic changes of life

Tachycardia is rather common. In a recent study of 320 patients with arthritis, seen on the hospital service of the Mayo Clinic, of those considered primarily infectious as contrasted to the metabolic or senescent type, 25 per cent had symptomless tachycardia at rest, without fever or a high metabolic rate, and 21 per cent had tachycardia, with either dyspnea or slight edema. These constitute not signs of hyperthyroidism, but of some cardiac injury, which may pass unrecognized by both patient and physician if there is no need for physical activity, and therefore, absence of the most important sign of myocardial damage, abnormal response to exercise. Pericarditis and endocarditis are more frequent complications than was formerly believed.

The metabolic rate in 80 per cent of the cases of chronic infectious arthritis in which the rates were determined, varied uniformly between +10 and -10 per cent. An occasional thyroid adenoma was noted, usually without associated hyperthyroidism, in four cases, however, the rate of metabolism was increased. The fact that a slightly increased metabolic rate is often beneficial in cases of arthritis has led us on two occasions, in the presence of a very mild hyperthyroidism of the adenomatous type, to postpone surgical intervention. This symptom was, however, carefully observed, to forestall any untoward developments.

**Case 2** — A man, aged thirty-eight years, had had an appendectomy when he was twenty-eight, and a tonsillectomy when he was thirty-eight. He had had a gonorrhreal infection at twenty-one. The chief complaint was of pain in the back and albuminuria. For the last year the patient had had a dull backache in the lower lumbar region, practically constant, but not progressive. His condition was worse in the afternoon and evening. When he was examined for life insurance rather marked albuminuria was discovered. This was persistent, and at times occasional red blood cells and casts were also found. A diagnosis of nephritis had been made, and the patient placed on a low protein diet.

Physical examination revealed a mild degree of chronic infectious arthritis of the sacro-iliac joints and ankle-joints. Three teeth were infected peripherally. The prostate was tender and enlarged, and a diagnosis of prostatitis, Grade 5, with macroscopic pus, was made. The systolic blood pressure was 110, and the diastolic 74.

Albumin, 2 and 1, was found in the urine, also an occasional cast and red blood cell, and occasional pus cells. There was no Bence-Jones protein, or orthostatic albuminuria. The blood counts, hemoglobin, blood chemistry, and water and concentration tests were normal. The phenolsulphonephthalein excretion was 65 per cent. On one examination, the urine was entirely negative before prostatic massage, but definitely positive for albumin after massage. After several days of massage, no red blood cells appeared in the urine. The diagnosis was chronic infectious arthritis, spondylitis, and albuminuria from prostatitis.

The decayed teeth were extracted, and treatment of the prostatitis was instituted, including instillations, massage and vesicle stripping. The patient is to return for examination in one year.

*Comment*—This case is interesting from two standpoints (1) the possibility of nephritis associated with arthritis, and (2) the rôle of the prostate in the causation of the arthritis and the albuminuria. True Bright's disease, or chronic glomerulonephritis, rarely results from or is associated with, chronic infectious arthritis. Six cases with this combination have been observed on the medical service at the Clinic. On the other hand, a focal nephritis primarily due to arthritis may be aggravated by succeeding infections of other types not related to arthritis, and cause the symptoms of nephritis to predominate. In 90 per cent of the cases of arthritis, albuminuria was present, mostly intermittently, but sometimes persistently. Occasional casts and red blood cells were seen. In only 4 per cent of the cases was there persistent albuminuria, reaching 2, this was associated with renal stone and gout (one case), pyelonephritis (one case), focal nephritis (one case), polyctythemia (one case), prostatitis (two cases), and myocardial insufficiency (one case). The phenolsulphonephthalein return was normal in 97 per cent of the cases in which the test was given. The blood chemistry was also essentially normal. A mild nephrosis without edema, or a mild focal nephritis, generally without microscopic hematuria, is therefore the common renal finding.

If moderate or severe albuminuria occurs, it deserves special

attention on account of its rarity. Multiple myeloma must be considered as a possibility, in this condition the complaint is usually "rheumatism in the legs or chest," and there is Bence-Jones proteinuria, and sometimes renal insufficiency.

The albuminuria in this case was of nonrenal origin. Focal nephritis may have existed previously, but could not be proved to be active. The rôle of the prostate is important here. In many cases of arthritis in men, the prostate is undoubtedly a grossly neglected focus. Chronic nongonorrhreal prostatitis is common, secondary to gonorrhea or sexual excess. It may not manifest itself for a long period, and may cause first lumbago or sciatica, and later a suddenly appearing spondylitis or widespread arthritis. Chronic prostatitis is often not disclosed until provocative massage is done.

Case 3.—A girl, aged nineteen years, came to the Clinic because of rheumatism. For seven years she had had arthritis, which started in the left knee, and spread to nearly all the joints of the body. She had been on crutches, or in bed nearly all the time, and felt that she was getting worse. Treatment elsewhere had included various types of baths, low carbohydrate diet, dilatation and curettage for leukorrhea, removal of the tonsils four years before, without a history of tonsillitis, and intra-articular injections of iodoform emulsion. No relief was obtained. Her general health had been good.

On examination partial ankylosis of the knees and hips, wrists and ankles was found. Flexor deformities were present, and the joints were swollen markedly with definite spindle formation. Marked anemia was evident. The heart showed a faint mitral murmur, systolic, and non-transmitted. Examination of the pelvis revealed cervical lacerations and a moderate leukorrhea. The foci except those of the pelvis were negative. The systolic blood pressure was 88, and the diastolic 52.

The hemoglobin was 53, 53, and 47 per cent (Dare) on three occasions, the erythrocytes numbered 4,120,000 and 4,060,000, and the leukocytes 12,000, the color index was 0.6 and 0.5. The blood chemistry findings were normal. The phenolsulphonephthalein excretion was 65 per cent. Gastric analysis revealed free acids 10, total 20. X-Ray examination of the joints revealed marked destructive arthritis. The Wassermann reaction was negative. The urine contained albumin 1 on several occasions. The diagnosis was chronic infectious arthritis, and secondary anemia.

Treatment for the pelvic condition consisted of boroglyceride tampons daily with an astringent douche of tannic acid and alum, and a slow hot-water douche (one gallon daily). The diet was limited to 3,000 calories. Fowler's solution and tincture of iodin were administered alternately and intermittently, according to the patient's tolerance. Baking and massage,

active and passive, were daily treatments. Buck's extension was used to correct the flexion deformity of the knees. Typhoid vaccine was injected intravenously. As a result of the treatment there was increase in the motion of the joints, a decrease of pain, and diminution of the swelling. On dismissal after six weeks the patient had made a "25 per cent improvement."

*Comment*—There was nothing to account for the secondary anemia except the chronic infectious arthritis. The grade of the anemia was greater than is generally seen in patients with arthritis, but is not as severe as that encountered in certain other similar cases. In one patient the hemoglobin was as low as 28 and 30 per cent, with erythrocytes numbering 1,620,000 and 1,210,000. Achlorhydria was also present, but no neurologic changes were evident. Pernicious anemia coincidental with the arthritis was suspected, but could not be demonstrated.

In the series of 320 cases 30 per cent had anemia 1 to 4, 25 per cent had anemia 1 (erythrocytes 3,500,000 to 4,000,000, hemoglobin 60 to 70 per cent (Dare), 60 to 80 per cent (Palmer)), 4 per cent had anemia 2 (erythrocytes 3,000,000 to 3,500,000, hemoglobin 50 to 60 per cent (Dare)), and 1 per cent had anemia 3 to 4. With anemia 3, the erythrocytes numbered 2,500,000 to 3,000,000, hemoglobin 40 to 50 per cent (Dare), with anemia 4, the erythrocytes numbered less than 2,500,000, the hemoglobin less than 40 per cent (Dare).

Case 3 is one of the most severe. The patient responded exceptionally well to hematonic efforts. As noted, achlorhydria was present. This may be present with or without anemia, and vice versa, although the more severe grades of anemia in the series were usually associated with either achlorhydria or low acids. Of 127 patients with the infectious type of arthritis on whom fractional gastric analyses were made, 28 per cent had achlorhydria, and an additional 19 per cent had definite hypo-acidity.

Case 4—A woman, aged twenty-six years, came to the Clinic because of "rheumatism." Her father and brother had arthritis. Ten years before, the patient began to have mild rheumatic pains in several joints. These were not constant, and never caused any inconvenience. Three years later they returned and progressed until they involved every joint in her body."

There was constant, marked aching everywhere "Colitis" was suspected last year, and an appendicostomy was performed. The colon was irrigated through it for five months, without improvement. Pneumonia and associated pericarditis complicated recovery from this operation. Tonsils and tage had been removed in three operations. Several teeth had been removed.

The systolic blood pressure was 100 and the diastolic 88 on one occasion, and 105 and 70 on another. The patient was anemic and thin, but there was no evidence of swelling of the joints, muscular atrophy, or typical spindle-shaped joints in any areas. There were, however, marked tenderness and soreness all over the body, with generalized arthralgia and myalgia. All motions were possible. The hands were cold and clammy. The suprACLAVICULAR glands and epitrochlears were definitely enlarged. The spleen was not palpable, but the abdomen was rather tender. The heart was not enlarged, but there was a systolic non-transmitted murmur over the mitral and pulmonic areas. Culture from the rhinopharynx revealed *Streptococcus viridans*. X-Ray examination of several joints was negative. There were traces of albumin in the urine. The erythrocytes numbered 4,360,000 and the leukocytes 8,600. The hemoglobin was 71 per cent. The patient was hospitalized for treatment and special study. A diagnosis was made of chronic infectious arthritis of a peculiar type.

The characteristic features in this case were (1) general emaciation with generalized myalgia and arthralgia, without limitation of the motion of the joints, and (2) lymphatic enlargement. Splenic enlargement, anemia, and leukopenia or leukocytosis were absent when the patient was admitted to the hospital, but a note was made that during the progress of the illness these should be expected. A few days later the abdomen became more tender, and there was a daily afternoon rise of temperature to between 99° and 102°, with a return to normal in the morning. In the course of the next two weeks the spleen gradually enlarged until it was felt 3 cm below the left costal margin. It was thick and hard and very tender. Associated with the enlargement of the spleen and the fever was a drop in the hemoglobin from 71 per cent to 35 and 40 per cent within ten days. The erythrocyte count dropped from 4,360,000 to 3,300,000. The leukocyte count dropped from 8,600 to 5,400 and then rose rapidly to 32,000. The differential count showed a polynucleosis. The blood platelet count was 224,000. An "endocarditis lenta" was suggested, but there was no evidence to support such a diagnosis. The blood cultures were negative. A biopsy of the epitrochlear gland showed inflammatory reaction and a staphylococcus was recovered. The fever gradually subsided with a return of the leukocyte count to 7,000 and 8,000. The erythrocyte count and hemoglobin remained low. The patient showed signs of marked toxemia and progressing exhaustion. The spleen diminished in size, but there was a residual soreness in the left upper abdominal quadrant. A transfusion caused no hematopoietic response or clinical improvement. An intravenous injection of mercurochrome was also given, but did not alter the general progressive failure, and the patient died.

Necropsy revealed chronic obliterative pericarditis and pleuritis, fatty changes in the myocardium and kidneys, perisplenitis, and splenomegaly with general lymphoid hyperplasia. There was no evidence of endocarditis. An

available joint which had been quite painful showed no signs of arthritic change. The heart was normal, but the spleen contained *Streptococcus viridans*.

*Comment*—This patient's syndrome is a form that might be called "Still's disease of adults." It is characterized by (1) generalized emaciation, (2) generalized pains in the muscles and joints, often without evidence of any objective or x-ray findings of arthritis, (3) lymphatic enlargement, (4) anemia with leukopenia or leukocytosis, and (5) splenomegaly. The anemia, abnormal leukocyte count, and splenomegaly developed after admission, during the course of an acute progression. The anemia, in the presence of splenitis and splenomegaly, suggested a splenic type. Splenectomy was advised not only because the spleen was probably a causative factor in the anemia, but also because it might be an important secondary focus of infection. The condition of the patient, however, seemed to contraindicate immediate surgery.

Osler mentioned splenomegaly associated with arthritis. Felty has recently reported five cases of splenomegaly, leukopenia and arthritis, and has suggested a coincidental arthritis and early Banti's disease.

Of sixteen cases observed at the Clinic with splenomegaly and arthritis, ten had anemia, eight hepatomegaly, and eight slight or no bony changes in the joints. Leukopenia and leukocytosis were evenly distributed. In Case 4 the number of leukocytes fluctuated with the activity of the splenic disturbance. Of our entire series of cases of arthritis the more marked anemias were seen in this small subdivision.

The term "splenic anemia" is in general used loosely and may include several syndromes. In this case the acuteness of the anemia, the rapid enlargement of the spleen, and the absence of gastro-intestinal hemorrhages precluded a diagnosis of the true splenic anemia of Banti's type. However, in several of our cases of arthritis with splenomegaly and anemia, the course has been much more chronic, and in such instances the exclusion of a true Banti's type of splenic anemia is not so easy. The absence of gastro-intestinal hemorrhages is an important dif-

ferential point, as such hemorrhages occur in a large percentage of cases of Banti's anemia

Cases such as Case 4 may represent an unrecognized clinical entity and not chronic infectious arthritis. A conservative opinion, however, is at present justified in view of the fact that the systemic nature of the infection in arthritis allows for so many combinations of pathologic processes

### DISCUSSION

With chronic infectious arthritis there may be what might be called "true complications." These include secondary anemia, achlorhydria, diminution of vascular tone with hypotension, myocardial and renal damage, pericarditis, pleurisy, and alterations in the metabolism of sugar. Many of these disturbances are mild in character, but in individual instances may dominate the clinical picture.

### TREATMENT

The treatment consists of the eradication of focal infections, the local treatment of joints, and measures directed to the general upbuilding of the patient.

The rôle of focal infection needs no extended comment. Infection should be sought in sinuses, tonsils, teeth, ears and mastoids, the gallbladder, appendix, prostate and pelvis. C. H. Mayo has often emphasized the fact that the large red tonsil is not always to be suspected as much as the small fibrous tonsil that has, through repeated infection, lost its powers of reaction and resistance. In all patients less than fifty years of age, tonsillectomy is advised, regardless of the past history or appearance of the tonsil. For patients more than fifty years of age, conservative treatment is adopted, especially if the arthritis seems to be of the senescent type associated with Heberden's nodes and mild hypertrophic changes, however, if the condition of the patient allows, or if the progression and type of the arthritis warrant it, the tonsils are removed. It is comparatively too harmless a procedure to neglect. Teeth with periapical infection are removed. Experience, and experimental bacterio-

logic studies seem to prove that a large percentage of devitalized roots of filled teeth are infected even though they may not show it Removal of all such teeth is therefore advised Sinuses are not commonly the source of arthritic infection, and chronic cholecystitis and appendicitis do not often cause arthritis, but such instances do occur and should be sought Whether primary or not, such infections should be removed in order to allow the body to fight the one disease alone As the prostate is frequently an unrecognized focus it may need a provocative examination to uncover the infection readily In all cases of spondylitis or arthritis starting with sciatica or lumbago special attention is given the lower genito-urinary tract whether or not there is a past history of gonorrhreal infection

Pelvic infection, as shown by Moench, and Walters, occasionally is the cause of arthritis Injections of gentian violet into the cervical os in addition to the use of tampons constitutes conservative treatment A cervical enucleation or hysterectomy may, however, be indicated Chronic constipation is always treated rigidly There is no definite proof that the intestines act as a focus of infection However, the institution of regular elimination by anticonstipation diet and noncathartic adjuvants, such as bran and mineral oil, is often an important point in restoring well-being

Baking and massage, active and passive, daily, are urged when the arthritic process is chronic The patient is advised to buy a baking machine and use it daily himself besides massaging his own joints when possible This is much more effective than sporadic, even though more efficient, professional service Diathermy sometimes affords more relief in acute and subacute cases As Fischer has said, "Motion is life for the arthritic patient," and the importance of exercise is stressed Occupational therapy is taught, such as basket weaving and knitting Correction of deformities is an orthopedic problem and will not be discussed, but their prevention is often accomplished by such measures Much credit is due to the care of the physiotherapists and the detailed training they give the patients, according to their individual needs

For pain salicylates, aspirin, pyramidon, atophan or sodium bicarbonate may be used. The chronicity of the disease precludes the use of opiates. Vaccine treatment, both of the specific and the nonspecific type, is used. Both seem equally effective in certain cases. The most useful nonspecific vaccine in our experience is triple typhoid vaccine given intravenously. It is made up in the hospital so that 1 c.c. of normal salt solution contains fractions of a minim of the vaccine. The initial dose is 0.2 minim of the vaccine, and it is gradually increased to 0.5 minim in 1 c.c. normal salt solution. Vaccine should not be given so often as to cause a chronic loss of appetite, or so strenuously as to cause exhaustion.

#### DIET

High calorie diets are prescribed as a routine except in cases of overweight. The majority of arthritic patients are much undernourished. No definite advantage has been noted with low protein or low carbohydrate diets, even in the presence of a lowered sugar tolerance. Most patients gain weight and strength, or at least increase their general well-being on a high calorie diet. Anticonstipation factors have been previously noted. Occasionally only specific food allergies will be noted.

If achlorhydria exists, one teaspoonful of dilute hydrochloric acid in water, gastron, or orange juice, is to be sipped during each meal. This may improve digestion, furthermore, it may assist in maintaining the gastric germicidal barrier, the importance of which should not be under-emphasized until its rôle is more definitely established. Other medication, such as Fowler's solution administered intermittently, according to the patient's tolerance, or from 5 to 10 minums of tincture of iodin in water three times a day, intermittently, according to tolerance, may help slightly.

#### EDUCATION

In a great many instances the physician only advises removal of teeth and tonsils, and gives the patient a pessimistic farewell. This is inadequate and is a *raison d'être* for the cultist.

Most of our arthritic patients have accomplished long-continued and painful hegiras in search of a "sure cure" They come to the Clinic as a last resort, poor in finances, in health, and in spirits Rarely do they know more than the most cursory details as to the character of their malady A very large percentage have at one time or another drifted to the cults With regard to osteopathy it is true that at least a certain amount of relief from the rational treatment with massage was frequently achieved, often for the first time In many cases treatment has been spasmodic and half-hearted, all the measures herein advocated being used at one time or another Our own method of treatment is limited to time-worn procedures However, the patient's response to the weekly educational lecture is gratifying In unscientific terms are taught the fundamentals in the structure of joints and the physiology of joint functions, the rôle of exercise, baking and massage, and the nature of focal infection and the relation it bears, removed or unremoved, to the systemic infection It is explained why certain procedures help and why others are of little use The patient is taught to consider himself in the same category as the tuberculous patient with regard to treatment, which must be general as well as local He is urged to carry out all possible procedures persistently no matter how relatively unimportant the individual procedure may seem He is instructed as to the chronic self-limiting nature of the disease, encouraged to be hopeful, and to fight optimistically the infection he carries With the restoration of partial peace of mind the patient is most grateful, even though his improvement is quite slow and measured

## CLINICAL TYPES OF VERTIGO

HARRY L. PARKER

A list of the various pathologic conditions producing vertigo is to be found in any of the modern textbooks of medicine. The array is both lengthy and formidable, and the average medical student has difficulty in picking out the particular disease picture that fits his vertiginous patient most closely. It would, therefore, be unnecessary, not to say tedious, to attempt to compile an exhaustive and comprehensive classification of diseases wherein vertigo is a prime symptom. It would be of more value to select a few cases and to discuss the relative importance of the symptoms in each. In such wise did Hippocrates recognize that "anorexia, heartburn, vertigo and a bitter taste of the mouth in a person free from fever indicate the want of purging upwards." Hippocrates' classification of diseases was rudimentary, but at least his grouping of symptoms and signs into readily recognizable pictures was of definite importance from the standpoint of the patient's future. A small group of patients with vertigo are worth studying, with the hope of determining the significance of that symptom.

### ILLUSTRATIVE CASES

Case 1.—A man, aged thirty-five years, came to the Clinic complaining of dizziness. For at least ten years he had had transient ringing noises in both ears. Nine months before examination, he had suddenly developed the sensation of dizziness with blurring of vision and uncertainty of balance. This gradually diminished, and disappeared within a few hours. Daily thereafter he had experienced the same sensation, lasting from a few hours to two or three days. He was unable to describe the feeling definitely, but there was no actual sensation of subjective or objective rotation. At no time had there been impairment of hearing, or disease referable to his ears. Occasionally, when the distress was severe, he had vomited sour material. Usually, after a meal he experienced burning distress in the abdomen. He

had always been a heavy smoker and troubled with constipation. Free purgation with calomel relieved his dizziness.

General physical examination did not disclose evidence of serious disease. The patient had septic tonsils, but his teeth were in good condition. There was no evidence of aural disease. A detailed neurologic examination revealed nothing unusual, and altogether there were few positive findings.

*Comment*—The patient represents a relatively common type seen from time to time in a large clinic. The complaint is usually of an indefinite sensation of dizziness without any rotary or tumbling character, and is either constant or vague in occurrence. Some of the patients have neurotic and unstable personalities, but many are evidently suffering from a definite, newly acquired disease which incapacitates them considerably. Migraine may play a large part in the history of such patients. Removal of foci of infection, treatment for constipation, and elimination of tobacco or alcohol may ameliorate the course of the disease.

**Case 2**—A man, aged forty seven years, came to the Clinic complaining of severe attacks of vertigo. Twelve years before, he had developed a high pitched tinnitus in the left ear, and progressive deafness. For nine years, he had been almost completely deaf and had constant tinnitus in this ear. A year before examination he had had an attack of vertigo which lasted about an hour. It was not repeated until six months later, and then the attacks became more and more frequent until they were a weekly occurrence. They came on so suddenly that the patient pitched forward and sometimes did not have time to save himself from falling flat on his face. Even while recumbent, sensations of falling forward continued, and thirty minutes after onset, forcible vomiting began. Vomiting and vertigo continued for an hour and then diminished in severity, so that at the end of two hours the attack was over and left him weak and exhausted. He has been awakened out of a sound sleep by an attack. There has been no change in his hearing and no increase in tinnitus during or between the attacks. He had become depressed and irritable and was in constant fear of an attack.

General physical examination revealed nothing unusual except a marked dental infection with septic tonsils, and deafness in the left ear. This deafness was not total as he could hear a loud shout on that side. Sounds, according to the Weber test, were referred to the right side, and bone conduction was reduced on the left side. His hearing of low "C" was greatly reduced and he could barely hear a "C<sub>4</sub>" tuning fork. There was no spontaneous nystagmus, and all responses to caloric stimulation of his semicircular canals came through intact. There was no evidence of otitis media at any time. A diagnosis was made of toxic vertigo, and the patient was advised to have his oral and tonsillar infection cleared up.

*Comment*—It is a startling and bewildering experience to have one's universe suddenly sway and whirl without appropriate warning or manifest reason. When accompanied by intense nausea and forcible vomiting, it is apt to shake the confidence of the average man in the fitness of things. Repeated at regular intervals, this experience creates a constant apprehension of being struck down in the midst of pleasure or important duties. A state of anxiety often is superimposed on the original disease, and turns intermittent suffering into a state of constant nervous debility.

The patient's condition in this case is extremely distressing, and usually in such a case there is little to account for the cause. In all such cases there may be no evidence of past or present disease of the middle or external ear. The normal health between sudden severe, yet transitory attacks constitutes the chief characteristic. This patient has a slowly progressive destructive lesion of the eighth nerve or its endings in the labyrinth. The process irritates as it destroys, hence the attacks, and when complete destruction of both vestibular and cochlear portions of the nerve is accomplished, the attacks will cease, probably leaving, however, total deafness with extinction of all responses to the labyrinthine tests. It is possible to have many variations of this process. The irritation may be transitory and leave no residue. It is relatively common for a patient to have one severe initial attack, resulting in a deafness that soon clears up. Succeeding attacks may be lighter and finally cease, with no residue. Again, there may be a single violent attack that leaves the patient permanently deaf and with a dead eighth nerve. Menière, in 1861, described only one phase of the condition, and wrongly attributed the process to hemorrhages into the inner ear. This interpretation, the result of examination of his one necropsied case, will not bear too closely scrutiny, and like other diseases that carry the name of a distinguished physician, Menière's disease is remembered as representing only a part of a large and varying clinical syndrome. Early observers saw only part of the manifestation of a disease process in their limited field of experience, and

hence arose a misleading nomenclature that leads to error in diagnosis

More recently, a toxic cause has been attributed in cases of paroxysmal tinnitus, deafness, vertigo, nausea and vomiting, and the degree of severity and permanency of residue is estimated in terms of the amount of toxin received at each attack. The initial attack may be relatively severe, but be followed by less severe attacks, it is then said the patient is getting better. On the other hand, each attack may be of similar or increasing severity until the eighth nerve is destroyed. The tinnitus and deafness may pursue an independent course, or they may be increased with each attack. The responses to labyrinthine stimulation by caloric irritation or turning may vary, just as does the deafness during and between the attacks.

Much speculation is rife as to the point of attack of this hypothetic toxin. The eighth nerve itself has been considered the point of assault by some, and the term "eighth nerve neuritis" is being used, by others the seat of damage is located in the nerve endings or organs of hearing and equilibrium in the inner ear. There is no proof for either assumption and further research is required to clear up so fine a point of differentiation. It is unlikely that the brain stem and connections therein of the eighth nerve constitute the affected area. For a disease to select one nerve structure in so crowded a region as the medulla and pons, and moreover for it to fluctuate in intensity, is without analogy in the pathology of the central nervous system. One might compare the clinical manifestations of toxic vertigo with the intermittent paroxysms of trigeminal neuralgia, but the analogy fails when one considers the absence of any permanent damage of the fifth nerve in the latter disease.

As to the source of the hypothetic toxin, the teeth, tonsils, prostate gland, and intestinal tract have been incriminated, sometimes rightly so since appropriate measures directed towards clearing up infection in these areas have relieved symptoms. Drugs, alcohol, tobacco, syphilis and mumps play a part in certain instances, but in others no source of toxicity can be found, nor any actual cause for the disease. Pilocarpin sweetens

have been used with a view to eliminating the toxin, but often with disappointing results. Too often, the disease process runs its own course, ending in complete disappearance of the attacks without permanent residue, or a gradual diminution in number and severity over a period of months or years, leaving an extinct eighth nerve apparatus.

The response to stimulation of the labyrinthine portion of the eighth nerve in patients with toxic vertigo varies with the degree of injury to the eighth nerve apparatus, and with different stages of the disease. The response may be normal, diminished, or absent; if absent shortly after an attack, it may return between attacks, as does the patient's hearing. Contrary to previous teaching, there may be a dissociation of hearing and vestibular function. A deaf ear may respond normally to caloric stimulation, and yet an ear with perfect hearing may not respond at all. Later, after the attack, the responses may return, and full function of the nerve be reestablished.

Clinically, the characteristic features of these cases of toxic vertigo are the clear-cut attacks and the complete absence of signs or symptoms pointing to any involvement of the central nervous system except that of the eighth cranial nerve. In the next case, however, a very different picture is presented.

**Case 3**—A woman, aged fifty-two years, came to the Clinic complaining of dizziness and unsteadiness of gait. Seven years before, she had noticed a persistent fluttering sound in her right ear which increased in intensity until five years before examination, when she became deaf in that ear, and noticed a numbness of the right half of the lips which gradually spread to the right cheek during the five years. She had recently had difficulty in retaining food in the right side of her mouth as it slipped out without her being aware of it. Four years before examination, she had experienced a constant sense of vague dizziness, more and more associated with an actual unsteadiness in gait and posture. This had been progressive to the time of examination. Two years before, occipital headaches had appeared, commencing early in the morning. They were of increasing intensity, but short in duration, and often were accompanied by transient blindness, increase in dizziness, and vomiting. Vision had failed steadily for six months, but there had been no diplopia.

General physical examination, aside from ophthalmoscopic and neurologic tests, disclosed little of importance. There was bilateral papilledema of the optic nerve head, of three diopters, with hemorrhages and exudates in the surrounding retina. Neurologic examination disclosed a marked hori-

zontal, vertical and rotary spontaneous nystagmus. There was complete deafness in the right ear to all tests, and correspondingly no response to caloric stimulation on this side. The left side was normal to all auditory and vestibular tests. The corneal reflex was absent on the right side and there was a subjective hypesthesia over the second division of the area of the fifth nerve on the right side. The most marked finding was ataxia in walking, the gait was reeling, cerebellar in type, and the patient had a tendency to fall to the right. The seventh nerve was normal in all its divisions. The diagnosis of a right acousticus tumor with increase in intracranial pressure was made and surgery advised. At operation the diagnosis proved to be correct.

*Comment*—This patient's history and findings present a marked contrast to those of the patient in Case 2, who had a history of intermittent attacks of vertigo with periods between, of more or less well-being. In Case 3, the history is of a remorseless progression, involving first the eighth nerve, later the fifth nerve, and finally the cerebellar tracts in the medulla and pons, with increase in intracranial pressure due to disturbance in the circulation of the cerebrospinal fluid. The patient's first complaint was tinnitus, and later deafness. Thus far there is an analogy between this case and Case 2, but thereafter, their courses were absolutely different, signs indicating a spread of the damage, due to the growing tumor, appearing in Case 3. The vertigo of the patient in this case is different. Subjectively it is more or less constant, and is merged with, and dominated by, an ataxia. Cushing expected to find a history of paroxysmal vertiginous attacks in the thirty patients with acousticus tumors whose cases he reviews. Although there was not uncommonly a sensation of giddiness relieved by recumbency, only one patient had a clear-cut paroxysmal attack of vertigo.

In toxic vertigo, the neurologic examination usually shows no other sign than involvement of the eighth nerve. During an attack, or rarely between attacks, there is nystagmus, but the lost corneal reflex, facial hypesthesia, ataxic gait, and optic papilledema are enough to suggest a more serious lesion than a toxic assault on the eighth nerve. The headaches, vomiting, ataxia and facial numbness are of more concern to the patient than her dizziness. Again, her dizziness is not so important

as her inability to walk straight, to balance, and to control her limbs. The vertigo had never been paroxysmal.

Patients with vertigo are often sent to a neurologist with the suspicion that the vertigo is a sign of early tumor in the posterior fossa. An acousticus tumor is suspected first because of the deafness and tinnitus, but often tumor of the cerebellum is in the mind of the observer. The intense violence of the attacks of vertigo, the vomiting, and the ataxia during an attack, seem *prima facie* evidence of something serious, but actually the more definite, clear-cut, and sudden the attack, the less likely it is to be due to something serious. Progressive destruction of any of the structures in the cerebellum or brain stem produces other and more prominent signs than vertigo.

**Case 4**—A man, aged thirty-seven years, came to the Clinic complaining of failing vision and headaches. As a boy in school, his clumsy gait had earned him the sobriquet of "fall over the chair." At the age of eight or ten years, he had had a bilateral suppurative otitis media with deafness, which improved within three weeks, but the right ear remained deaf. He had had no discharge from the ears since then. Seventeen years before examination, he had noticed a clumsiness in using his right hand, which progressed until he had to learn to write with his left hand. At the same time, he noticed slight awkwardness in using his right foot and leg. This trouble became stationary after eight or ten months and remained so until three years before coming to the Clinic, when it began to progress in severity, and twelve months before, he had developed headaches, diffuse at first, but later localized to the right occiput. These headaches, at first intermittent, had become constant with acute exacerbations during the last three months of illness prior to the examination here. During these paroxysms of intense headache, which lasted only from two to five minutes, he experienced dizziness for the first time. It was not definite in character. There was no sense of rotation or falling forward or backward. The dizziness was so inextricably mingled with the headache that the patient was not able to describe it clearly. The incoordination of his right arm and leg increased also during a paroxysm of headache, and he was generally ataxic. Three months before, his vision had become blurred, reading had become difficult, and all the other symptoms of headache, ataxia, incoordination and dizziness were becoming progressively more severe.

On examination, the patient was found to have edema of both optic nerve heads, of five diopters, with punctate hemorrhages around the optic disk, but his vision was still fairly well preserved. He had a definite horizontal, vertical and rotary nystagmus, and his hearing in the right ear was greatly impaired. He was ataxic, reeling to the right, but could walk without assistance. Incoordination of the right upper and lower extremities was quite

marked, and he failed to perform accurately the usual finger to nose and heel to knee tests. There was little wrong with the left upper and lower extremities except for the general ataxia. Percussion over the right occipital bone was painful, his headaches were the most severe in this region. Caloric irritation of his right ear produced no responses except a mild vertigo on stimulation of the horizontal canal. Responses from the left side were normal. This might be interpreted as indicating a residue left from the suppurative disease of the ear, or involvement of the vestibular tracts during the more recent trouble. The escape of one part of the vestibular tracts, that is, the right horizontal canals with damage to the others and to the cochlear part of the eighth nerve, according to modern views of the Barany test, might suggest a lesion of the brain stem rather than of the end organ.

A diagnosis of right cerebellar tumor was made and surgical exploration advised. At operation a relatively large cerebellar cyst, 3 by 4 cm in diameter, was found in the right cerebellar lobe. Thirty cubic centimeters of a yellow gelatinous fluid was extracted, and stringy necrotic brain tissue was easily curetted from the cyst wall which was apparently the remains of a degenerating glioma of many years' standing.

*Comment*—Dizziness was again a relatively minor sign during the progress of the disease. Damage to the right cerebellar lobe may produce the focal signs of homolateral ataxia and incoordination, as in this case. This was the prominent symptom for many years until increased intracranial pressure brought more signs in its train. Dizziness accompanied the severe headaches during the last three months, and it was apparently due to the rise in intracranial pressure. It was not an early or a focal symptom, nor was it of any definite character.

In the past it was thought that cerebellar tumors produced a type of vertigo of localizing significance and that the rotation of surroundings in relation to the patient, or vice versa, indicated an extra- or intracerebellar tumor. More recent observers deny that this occurs frequently enough to be of practical value. Weisenburg doubted whether the type of vertigo associated with cerebellar tumors could often assist in the localization of the tumor. According to his observation the vertigo is more likely to be vague and indefinite, and can never be used as a focal symptom and for purposes of localization. In Case 4, its localizing value was nil, since it was probably more the result of general increased intracranial pressure than of any local pressure effect of the tumor.

Tumors filling the fourth ventricle and arising from its walls may produce paroxysmal, or continuous dizziness, even without signs of increased intracranial pressure. In a recent study of tumors in this region, I discovered that in fourteen patients with the disease, vertigo was prominent in the histories of four, and in one it had preceded all other symptoms by nearly three years. The latter described it as a sensation of constantly looking through at a heat haze. It interfered with his walking and working, and suddenly turning his head to the right produced an exacerbation of this dizziness. Ataxia appeared only in the last six months of the illness, and signs of increased intracranial pressure appeared even later. Tumors of the fourth ventricle are relatively rare, and vertigo was marked in only a small number of these. Vomiting was the most marked symptom, in the majority it was the earliest, and was associated with headaches. Vertigo, if it occurred at all, was a later symptom. Sudden attacks of vertigo due to a cysticercus cyst free in the fourth ventricle have been described by Bruns in Germany, but cysticercus disease is rather rare in this country.

Case 5.—A man, aged sixty-three years, came to the Clinic complaining of a numb burning sensation in his left arm and leg. Ten weeks before, at 10 a.m., he had developed a sudden attack of vertigo with a sense of rotation of surrounding objects. It lasted one or two minutes and disappeared as suddenly as it had come. At about 9 p.m. the next day, with the same suddenness, he vomited and continued doing so for two or three hours. About five minutes after the vomiting commenced, vertigo came on again with the sensation of a clockwise rotation of objects. The vertigo also lasted several hours, and attacks continued during the next four weeks whenever the patient sat up or turned suddenly, so that through fear he remained in bed. The third day after the onset of trouble hiccup made its appearance, and there were paroxysms of this almost every hour for ten days. There was a convergent strabismus of the right eye with diplopia at the onset, and the patient was so hoarse that he could only speak in a whisper. Both of these troubles improved during the next six months, but the hoarseness did not disappear altogether. A week after the onset, a burning numbness over the left leg and arm developed, which has persisted and formed his chief complaint. During the four weeks the patient was acutely ill with vertigo, vomiting and hiccup, although there was marked prostration, he did not lose consciousness or have headache. At the time he left his bed and for the first time after his illness, he had some trouble in controlling his right arm and leg, but this had practically disappeared.

Physical examination revealed a well preserved, obese elderly man with moderate peripheral arteriosclerosis. His systolic blood pressure was 145, and his diastolic 95. Ophthalmoscopic study of his eye grounds disclosed moderate retinal arteriosclerosis. There was a narrowing of the right palpebral fissure, recession of the globe of the eye, and reduction in the size of the right pupil. There was no noticeable ocular muscular weakness, although, when a red glass was used, he developed a crossed diplopia on looking to the right. There was slight bilateral ptosis, more marked on the right. The patient had diminished hearing in each ear, commensurate with his age. His right vocal cord was paralyzed and the left side of the body below the clavicle was anesthetic to pain and heat. The reactions to other forms of stimulation, including tactile, were normal. Both corneal reflexes were normal. The gait was only slightly ataxic, and there was no incoordination of the upper extremities. There were no changes in muscle strength or tendon reflexes. Mentality was normal.

*Comment*—In a study by Wolzman of 146 patients with cerebrospinal arteriosclerosis, dizziness was complained of in 57 per cent. In 118 per cent it was a prominent complaint. Altogether, it was the most common symptom in the whole group, and seems to be a usual symptom among aged and arteriosclerotic patients. Ordinarily, the vertigo is indefinite in character, and either comes in transitory mild attacks following changes in posture, or as a more or less constant sensation. Sudden severe attacks with nausea, vomiting, and falling, are not so common unless part of a vascular accident in the brain, leaving a more or less permanent residue. In this case the brunt of the damage was borne by the upper medulla and pons. The cause was probably thrombosis of one of the smaller vessels in that area, possibly the posterior inferior cerebellar, although the damage was somewhat less than that produced when this artery becomes thrombosed. A small area of softening on one side of the medulla will injure a fairly crowded area. The vomiting, hiccup, and paralysis of the vocal cord were due to damage of the nucleus ambiguus. The vertigo was due to irritation of the vestibular nuclei and vestibulo-spinal tract. The homolateral ataxia was due to involvement of the cerebellar tracts, and the heterolateral dissociated anesthesia to destruction of the spinothalamic fibers which cross in the cord. The right convergent strabismus was due to a temporary lesion of the sixth nerve nucleus, and the Horner's syndrome of the right

eye to disturbance of the sympathetic tract in the medulla. The more permanent residual, and therefore severest, blow was around the nucleus ambiguus and spinothalamic tracts constituting the syndrome of Avellis. The succession of attacks, the first slight, the second severe, the intense nausea, vomiting and vertigo without loss of consciousness, above all the prolonged and persistent paroxysms of hiccup in an elderly patient with aphonia and paralysis of the vocal cords are characteristic features of vascular lesions around the medulla.

It is common for arteriosclerotic patients to talk of dizziness when it is reasonable to assume that they mean syncopal attacks or some phenomenon other than vertigo. Be that as it may, it is hard to be sure in many instances what significance these attacks have. Probably, in most instances, there is a temporary vascular insufficiency of some portion of the brain. After a series of such attacks, one often finds residual weaknesses of the extremities, increased reflexes on one side, a speech difficulty, or slight mental impairment. The lesions in such instances probably are small lacunar hemorrhages, or areas of softening. Bilateral deafness and bilateral tinnitus are the rule in cases of cerebral arteriosclerosis, and these signs with retinal arteriosclerosis, disturbance of vibratory sensibility to the lower extremities, incontinence of urine, and the patient's general appearance, are common enough to suggest that the vertigo is due to cerebral vascular degeneration.

It has been obviously impossible to demonstrate all the diseases in which vertigo is a symptom. Of those remaining, the number is legion, but as a whole they are either too obscure or too obvious to merit prolonging the discussion. The outstanding feature, in most instances, is the presenting disease causing the vertigo, such as suppurative labyrinthitis, aortic insufficiency or multiple sclerosis. It has been sufficient to select a few types of vertigo and to study these in terms of the general disease pictures, the underlying pathologic alteration, and the prognosis of the particular disease wherein vertigo appears as a symptom.



## HEADACHES

HENRY W. WOLTMAN

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It is probably true that certain persons never have headaches. The rest of mankind are more or less intimately acquainted with the symptom. As with the Ancient Mariner, it appears when we want it least, and gives advice when we do not ask for it. Despite its great frequency, little is known of the etiology, and almost nothing of the subtle mechanism of its production. A survey of the literature leaves us bewildered, and with the conviction that most texts represent only compilations of the past.

I shall not attempt here to cover all phases of the problem, since this has been done well many times, but shall illustrate some of the more common types of headaches, by the presentation of cases, for the purpose of discovering what remains of the subject when shorn of theory, and viewed in the light of clinical experience. This curt and didactic method is necessary, when one is sufficiently immodest to discuss a large subject of which so little is known.

Much has been written concerning anemic headaches, hyperemic headaches, gastric headaches, and ovarian headaches. Certain writers assert that eye-strain causes more than 90 per cent of headaches, others would have us believe that the nose is responsible for every headache. What, then, shall we believe of diabetic headaches, uric acid headaches, growing headaches, and reflex headaches?

We must return to the source of our text, which is the patient, and let him tell us about his complaint. Seven points at least should be determined in our inquiry (1) location, radiation and depth, (2) duration, (3) frequency, (4) character, (5) in-

tensity, (6) progress, and (7) associated symptoms and relation to other functions. Many satisfactory classifications of headaches have already been made, and the following arrangement is based on points of importance, and does not indicate the need of revising earlier classifications. Probably the first point to be determined in a given case is whether or not the headache is the result of an organic disease.

#### HEADACHES ASSOCIATED WITH ORGANIC DISEASES INVOLVING STRUCTURES OF THE HEAD

Headaches may be associated with various diseases involving the structure of the head: (1) diseases of the brain and its coverings, particularly such conditions as tumor, abscess, encephalitis, sinus thrombosis, meningitis, tuberculosis, syphilis, vascular diseases, hemorrhage, trauma, and lumbar puncture, (2) diseases of the special sense organs, such as the eye, including tumors, inflammatory processes, glaucoma, refractive errors, the ear, remembering that intracranial extension is not uncommon, the nose, not overlooking malignant disease of the nasopharynx, sinus diseases, vacuum headaches, and other inflammatory and structural disturbances, and (3) diseases of extracranial structures, such as the muscles of the scalp and the fascia.

That a careful history and examination are the only methods of reaching a correct diagnosis in these cases is obvious. Mistakes are common, as evidenced by the numerous, futile attempts made to relieve headaches due to tumor of the brain by refraction, and by operations on the nose.

**Brain tumor.**—Headache may be quite absent in cases of brain tumor, but as a rule it is a severe and prominent symptom. It is most characteristic when it occurs early in the morning, often at three or four o'clock, and awakens the patient from sleep. Why this occurs so frequently is not known, but pain in cases of spinal cord tumors exhibits the same behavior. If inquiry is pursued further, it may be learned that the patient vomits precipitately before breakfast or during a meal, and if it can be demonstrated also that the pulse becomes slow

or irregular during the headache, then the reasons for suspecting increased intracranial pressure are clear.

The location of headache in cases of brain tumor is often of considerable value, if interpreted cautiously, regardless of all that has been said to the contrary. This is notably true if the pain is localized, and if it is sharp and cutting in character. Bilateral frontal headaches convey little information, since they often result from secondary hydrocephalus; occipital headaches, on the other hand, when accompanied by rigidity of the neck, may lend the necessary support to other evidence at hand pointing to a lesion in the posterior fossa. Local tenderness on percussion may be of value, although I have been seriously led astray by it. The patient presented only an intense, sharply defined, right frontal headache, with marked local percussion tenderness and choked disc, a tumor of the right frontal lobe was suspected. The patient contracted influenza while under observation, and died. Fortunately he had not been operated on, but necropsy disclosed a marked erosion from pressure in the right frontal area, where the skull was reduced to the thinness of paper, and a pultaceous extracerebellar tumor on the left side.

It is often said that headache due to an organic disease, notably brain tumor, is constant. If any statement may be made, I would say that periods of remission are more characteristic of headache due to brain tumor, and that a wholly uninterrupted headache of long duration in a patient not obviously ill, usually turns out to be psychoneurotic in origin. To the three cardinal and classical symptoms of brain tumor, namely, headache, choked disc, and vomiting, should be added a fourth, fully as important, namely, a story of progression.

Auerbach stresses combinations of various types of headaches, and it is important to bear this point in mind. A patient who has had migraine for years may also develop a brain tumor or hypertension. The migraine may cease on the appearance of the second type of headache, or the two may continue pari passu. The patient is usually able to distinguish the two kinds of headache without difficulty.

## ILLUSTRATIVE CASES

Case 1 Migraine and right acousticus tumor—A woman, aged forty-two years, came to the Clinic in December, 1922, complaining chiefly of headache and dizziness, of three years' duration. Her headaches dated from childhood, they were occipital, associated with vomiting, and periodic, usually accompanying menstruation. This type of headache had stopped spontaneously about five years before the patient came to the Clinic. They closely resembled the father's sick headaches. Four years before, she had consulted a physician because of crackling noises in the right ear. Her hearing became impaired, within six weeks she could not hear a watch tick, and at the end of one year the right ear was completely deaf, and the noises had disappeared. Three and one-quarter years before she experienced attacks of transient, oblique diplopia. Three years before, right occipital headaches appeared, these extended from the lower portion of the occiput almost to the bregma, the worst pain being located 5 cm. above and behind the ear, these headaches at first came at intervals of two or three hours, but recently had become more frequent, lasted from five to twenty minutes, were mild or excruciating in intensity, and usually much worse early in the morning, aching or cutting in character, and recently had been associated with a sensation of weakness and impending syncope. Three years before she had had occasional slight vertiginous attacks, lasting two or three minutes. One and one half years before, a "dead, wooden sensation," which was continuous and became gradually worse, appeared over the right side of the face, and she also lost the sense of taste over the right half of the tongue. A slowly progressive right facial palsy appeared at the same time. Speech became slow and indistinct, and the patient experienced some trouble in writing. For one year, she had noted difficulty in swallowing saliva, and during the paroxysms of pain there was a sense of choking and suffocation, and also difficulty in starting the flow of urine. Six months before, about once a day, usually before breakfast and during an attack of headache, she would vomit abruptly, and without nausea.

General examination was essentially negative, including an x-ray of the skull. There was a keratitis on the right, the haziness of the cornea making it impossible to see the fundus on the left side. A colored disc of three diopters and some hemorrhages, vertical nystagmus on looking upward, a slow coarse nystagmus on looking toward the right, and a fine rapid nystagmus on looking toward the left, moderate right facial palsy, and numerous fibrillary tremors in this territory, loss of taste on the right half of the tongue, complete deafness of the right ear, moderate ataxia, with slight decrease in tonicity, moderate adiakokinesia, slight dysmetria, and a very slow movement tremor of the right upper and lower extremities. The speech was ataxic. The patient staggered somewhat in all directions on walking, however, the importance of this symptom was hard to evaluate since she was very well. The head was tilted so that the chin approached the left shoulder.

A diagnosis of right acousticus tumor was made and on exploration a neurofibroma was found and completely removed. The patient died five days later, necropsy disclosed multiple small hemorrhages into the cerebellum and pons and bronchopneumonia.

**Case 2 Cerebellar glioma with short history and few objective findings**—A boy, aged eight years, was brought to the Clinic in August, 1924, because of headache. The patient's health had been excellent until seven weeks before examination. July 5, he did not feel well, and two days later developed a severe left occipital headache. This recurred paroxysmally almost daily, lasted from one to four hours, and was aggravated by coughing, sneezing, and jarring of the head. Aspirin relieved the pain considerably.

The examination was essentially negative, but it was noted that the pulse rate occasionally dropped to 56, and was particularly slow and irregular when the headache was most intense. There was a suggestion of vertical nystagmus, very slight incoordination of the left upper extremity, and a slight movement tremor of both upper extremities. Examination of the fundus was negative. A diagnosis of cerebellar tumor, involving chiefly the left cerebellar lobe, was made.

On exploration, the left cerebellar lobe was found to be larger than the right, and a soft, purplish gray mass, evidently a glioma, was found on separation of the convolutions.

In Case 3 a complicating migraine and the paucity of objective findings introduced certain difficulties. The x-ray revealed a shadow which coincided with the location of the pain, which illustrates the occasional value of radiography in these conditions.

**Case 3 Calcified tumor of the left posterior parietal region**—A minister, aged fifty-four years, presented himself for examination in September, 1924, complaining of pain in the left side of his head. His mother and a sister also had headaches. Since childhood the patient had had intense, bilateral, frontal headaches, which came on every five or six weeks, lasted one or two days, were accompanied by nausea, and occasionally by vomiting. These headaches had gradually diminished during the last ten years, but had been replaced five years before by left-sided headaches of the same frequency, which became gradually worse. During the last year, they had been constant, incapacitating the patient one-third of the time. These "new" headaches extended from the left eye to the occiput, included the mastoid region, and radiated to the left shoulder. The pain was of a "heavy, dragging, bearing-down" type, interspersed by sharp, cutting pains of great intensity, particularly in the left occipital region. There were no scotomas or vomiting, and no history of injury to the head.

The general examination was essentially negative, save for the finding of a calcified area over the left posterior parietal region. Exploration revealed a calcified mass 5 cm below the surface. Following decompression the patient was completely relieved of the pain.

**Brain abscess**—The history in a case of brain abscess is typically one of a sudden and stormy onset, perhaps with con-

vulsions, pain in the head, rigidity of the neck, fever, and leukocytosis. A spinal puncture at the time of onset may give evidence of meningitis. A period of relative quiescence and apparent improvement follows, corresponding to the stage of recovery from the diffuse initial onslaught, and of encapsulation. Occasionally there may be complete symptomatic recovery, but usually, after several weeks, extension of the trouble, or rupture of the capsule may be anticipated. This condition has been thoroughly discussed by Adson.

**Arteriosclerosis**—Arteriosclerotic headaches are often diffuse, more or less continuous, as a rule not severe, the sensation being of pressure rather than of pain. The associated confusion, vertigo, and lack of attention, and the objective findings, establish the diagnosis.

**Lumbar puncture headaches**—The characteristics of lumbar puncture headaches, with symmetrical, occipital and frontal "drawing" pain, present on arising, disappearing on lying down, are too well known to call for further comment.

**High cervical cord tumors**—High cervical cord tumors may be associated with pains in the head, as in the following case.

**Case 4**—A woman, aged thirty-two years, presented herself for examination in May, 1923, because of right-sided headaches which had begun three years before, four months prior to the birth of a child. The headache consisted of a "heavy, numb" pain in the right occiput, which was almost constant and increased steadily in severity, it was usually present in the morning on awakening. Eighteen months before, sharp pains had developed at the vertex, these would awaken the patient at three or four o'clock in the morning, and were usually brought on by fatigue or by jolting, as when riding in an automobile or in a street car. One year before, a sharp knife like pain, the most distressing of all, began over the right eye, this too came on almost every morning at three or four o'clock. All of the pains diminished after the patient got up and moved around, which she did at this early hour. By six o'clock they were as a rule entirely gone, and she would feel well for the remainder of the day, and fall asleep at night without trouble. Six weeks before, numbness and clumsiness of the right hand appeared. She found it difficult to pick up a needle. The right leg didn't "feel just right," and tired easily, although she did not think that her legs were actually weaker.

The general examination disclosed a five months' pregnancy. The right upper and lower extremities were slightly weak, with increase in tonicity and diminution of speed, more marked in the upper than in the lower. The

tendon reflexes were increased, the right Babinski reflex was strongly positive, the left slightly so, the gait was slightly spastic on the right, there was partial impairment of joint sensibility and of stereognosis in the right hand, the pain and temperature sensibilities were moderately impaired over the left thigh, leg and foot. The spinal puncture findings were negative. A rudimentary cervical rib on the left side was disclosed by x-ray. A diagnosis of high cervical cord tumor was made. The patient was advised to let pregnancy pursue its normal course, and to return for examination in November, 1923.

On her return, in November, the right hemiplegia had increased, the right arm being almost completely paralyzed, pain and temperature sensibility were now normal over the left leg, but were completely lost over the left upper extremity, left half of the trunk, and the upper portion of the thigh, being practically normal around the buttocks, vibration and joint sensibility were absent over the right upper extremity, tendon reflexes were all slightly increased and equal on both sides, the plantar responses remained as before. Exploration was advised.

An endothelioma, 2 cm long by 1 cm in width, arising from the arachnoid and adherent to the dura, located on the right side just above the exit of the great occipital nerve and extending to the margin of the foramen magnum, was removed. Since then the patient has recovered health almost completely.

In this case the occipital pain probably represented a root pain, due to involvement, by the tumor, of the nerves distributed to this area of the head, the supra-orbital pain may well have been the result of pressure on the descending spinal root of the fifth cranial nerve.

**Injuries to head—Headaches which follow injury to the head** are often continuous and persistent, and are usually attributed to the injury, by the patient. They are hard to explain. Some are probably the result of injury to the cranial contents, whereas many are undoubtedly hysterical in origin. More will be said of this subject, and a case history presented under Group 5.

**Ocular headaches**—Most of the so-called ocular headaches referred to, but not described in texts, are probably nothing more or less than attacks of migraine of varying severity. Certain ophthalmologists assert that more than 90 per cent of all headaches are due to eye-strain. Possibly this is owing to the fact that their practice is almost exclusively ophthalmologic, and that many of their patients themselves recognize a constant relationship between the appearance of their headaches and use

of the eyes, and the freedom from headaches when their eyes are at rest. For a general type of practice, however, such as that seen at the Clinic, in which patients come because of headaches due to any cause, this figure is entirely too high. It is the opinion of the consulting ophthalmologists at the Clinic that only 4 to 10 per cent of headaches are due entirely to eye-strain, and may be relieved completely by correction of refractive errors. There is a large group of persons whom we may designate as migraineous, who seem to have particularly sensitive and unstable nervous systems, and in whom errors of refraction constitute only one of the multitude of precipitating causes of headache. In these patients correction of eye-strain may lessen the number of attacks, but rarely abolishes them entirely. Obviously, what has just been said does not apply to headaches resulting from such conditions as orbital tumors.

**Nasal headaches**—The endless file of patients having migraine and continuing to have migraine after operation on the nose of one kind or another, has convinced me that unquestionably too much disappointment and violent objection is directed against the preordained architecture of the nose. Headaches due to sinus infections, structural deformities interfering with the physiologic processes of ventilation and drainage and vacuum frontal headaches, however, call for appropriate treatment which is followed promptly by relief.

**Sphenopalatine neuralgia** as a clinical entity is rare. Many of the published case histories are cases of typical migraine. Tic douloureux cured by sphenopalatine injections is not tic douloureux. When asked, "What is migraine?" we must admit that we do not know. It is significant, however, that of about 7,000 patients seen annually in the Section on Neurology of the Clinic, many of whom have headaches, no definitely proved case of sphenopalatine neuralgia has been seen. The local test applications were made by expert rhinologists, who found that a dry swab, water or cocaine applied to the region of the ganglion gave equally satisfactory results. It would seem that the appellation sphenopalatine neuralgia, at the present time, represents merely a new label on an old tin can. If true neu-

ralgias have their seat in a ganglion, then it is conceivable that there might be a sphenopalatine neuralgia, but if so, it should present a clinical syndrome as sharp and clean-cut as trigeminal neuralgia. Such a syndrome has not yet been delineated.

**Rheumatic, indurative, or nodular headaches**—These are probably caused by inflammatory changes in the muscles overlying the skull. The pain, which is superficial in location, is dull and aching, and is aggravated by cold drafts and by prolonged tension on the muscles overlying the skull, as when the head is held forward in reading or sewing. Points of tenderness are common. The headaches are usually relieved by heat and massage, and are often associated with rheumatic pains elsewhere. At the Clinic, we have not been able to palpate nodes of induration, said to be so characteristic of the condition.

#### ILLUSTRATIVE CASE

**Case 5**—A woman, aged forty-one years, came to the Clinic in June, 1924. For about eight years she had suffered from aching pains in the neck, which radiated to the shoulder and back. At the time of onset, the muscles of the lower extremities were also painful. The pains were much aggravated in 1923 by sitting for an hour in front of a garage on a cold day, without hat or coat. After this, they became worse on exposure to cold, and whenever the patient was compelled to sit in one position for a long time, as when listening to a sermon or reading. They were greatly relieved by heat.

General examination revealed infected teeth and tonsils, hypertrophic arthritis of the sacro-iliac joints and of the lumbar spine, and tenderness of the nuchal muscles. A diagnosis of rheumatic headache was made. Elimination of infected foci and prolonged applications of heat to the painful areas, followed by heavy massage, brought relief.

**Acromegaly**—In acromegaly we sometimes see diffuse and persistent headaches, this has probably the same significance as pain arising from other parts of the body, such as the hands, which are undergoing rapid structural alterations. Headaches from other causes, such as tumor, occur in acromegaly also.

#### HEADACHES ASSOCIATED WITH INFECTIOUS AND TOXIC DISTURBANCES

**Acute infections**—Many of the acute infections, such as smallpox, scarlet fever, poliomyelitis, and trichiniasis, often are accompanied by violent headaches.

Nephritis—Like other toxic headaches, those associated with nephritis are usually bilateral, vaguely frontal or general in location, more or less continuous, aching in character, mild or severe. They are most common in cases of chronic diffuse glomerular nephritis, and may be due to retained products. In this connection the work of Hewlitt, Gilbert and Wickett is exceedingly interesting and instructive. These investigators found that the ingestion of sufficiently large quantities of urea to raise the blood urea to 150 or 160 mg. for each 100 c.c. produced a dull headache and a feeling of lightness as the first symptoms. One of these subjects was migraineous, and the experiment seemed to precipitate an unusually severe, but characteristic attack of migraine. The appearance of a toxic type of headache preceding an epileptiform seizure should make us think of the possibility of nephritis. The seizure of so-called essential epilepsy appears abruptly, with or without preliminary aura, loss of consciousness is instantaneous. A patient having an epileptiform convulsion while playing cards will often tell us what card he intended to play before he lost consciousness. I have learned from internists who are especially interested in the study and treatment of nephritis, that there are two conditions in which nephritic headaches are prone to occur (1) when there is considerable retention, as indicated by high blood urea, and (2) when there is an associated hypertension. Often the two are combined. The headaches of hypertension have certain characteristics which distinguish them from toxic headaches, these will be discussed later.

Poisoning—Undoubtedly headaches may result from poisoning by some or all of the following substances: amyl nitrite, ether, chloroform, hydrogen sulphide, carbon monoxide, tobacco, morphine, alcohol, caffeine, and lead. Whether these headaches are directly due to the toxic agent, or indirectly due to a secondary toxin produced by the body, is not certain.

#### HEADACHES REFERABLE TO DISORDERED CIRCULATION

Here we may include the headaches noted in hypertension, in passive congestion, and in polycythemia.

**Hypertension**—The headaches of hypertension are rather characteristic in that they tend to appear early in the morning, and usually wear off after the patient gets up, they are as a rule bilateral, occipital or frontal, and tend to occur almost daily, in contradistinction to most types of headache. They are said, by Mackenzie, to occur on change of posture, but they do often awaken the patient from sleep. They may resemble the headaches of brain tumor even to the extent of having associated choked discs (Wagener and Keith).

**Passive congestion**—Mediastinal tumors may produce passive congestion of the head by interference with the return circulation to the extent of producing marked conjunctival edema. Headache is not uncommon.

**Polycythemia**.—In polycythemia the blood-vessels may not be sufficiently large to accommodate all of the blood. In one case seen at the Clinic the blood volume was two and one-half times the normal amount.

#### MIGRAINE AND ITS VARIATIONS

The most striking manifestation of migraine is headache, however, there are an abundance of other symptoms, such as ocular manifestations, notably scotomas, paresthesias, paryses, gastro-intestinal disturbances, vasomotor reactions, and psychic fluctuations, so admirably discussed by Moersch.

Doubtless many of the mythologic types of headaches which must have bewildered writers, and certainly confound readers, belong to this category, namely, anemic, congestive, nervous, habitual, familial, adolescent, anaphylactic, periodic, bilious, neuralgic, liver, ovarian, uterine, menstrual, pelvic, gallbladder, gastric, intestinal, ocular, nasal, sphenopalatine, diabetic, uric acid, pituitary, reflex, sympathetic, and other headaches. Almost every type of treatment and operation has been resorted to for its relief, including the removal of an eye, since the pain seemed to lodge there, and trephine of the skull.

In all probability, migrainous attacks may be precipitated by a great many different factors, which means that the actual

underlying cause is wholly unknown, and probably the result of some instability inherent in the organism. Jelliffe gives an excellent review of the subject. Statistical details may be found treated more extensively in Lewandowsky's "Handbuch der Neurologie." The condition is usually regarded as hereditary, and a family history of headache undoubtedly aids in its diagnosis. The proof of heredity, however, in such a prevalent affection, as stated by Jelliffe, is difficult.

Often one hears that a headache "may turn into migraine," "that it was not migraine, because the patient did not vomit." It should not be forgotten that migraine is protean in its manifestations, that the attack may be mild or severe, may be evidenced by only a dull headache, by a transitory scotoma, by a passing period of mental depression and "loginess."

**"Anemic headaches"**—The references to "anemic headaches" are many. Auerbach, in his book on headache, says, with reference to constitutional diseases "First and foremost in this connection must be mentioned the various forms of anemia, and the most frequent cause in proportion to incidence is chlorosis." Ross says, "Anemic headache is of a dull tension character, usually affecting the temples, brow and vertex, and extending along the sagittal suture. It is relieved by rest in bed and the recumbent posture, and rendered worse by long maintenance of the erect posture. There is a disposition to faint, general pallor, palpitation, dizziness, and uterine disturbances in chlorotic females. All causes which exhaust the nervous system, such as anxiety, night watching, and sexual excesses, aggravate this form of headache." Oppenheim says that anemia, whether chlorotic or occasioned by loss of blood, is almost regularly accompanied by headache, which is usually dull and pressing. On the other hand, Dercum says, "Finally it may well be doubted whether head pain constitutes a symptom or at least a prominent symptom of cerebral anemia. Cerebral hyperemia as a cause of headache has suffered an almost similar fate." In an interview with a prominent internist who probably has seen more cases of anemia than anyone else in this country, he remarked "I think you can use the red pencil on that. There

is no such thing as an anemic headache, either in primary or in secondary anemias. Of course people having anemia may have headaches, as do others, but it is not a part of the disease."

"**Diabetic headaches**"—Regarding "diabetic headaches" another internist with a large experience with diabetes, remarked, "I never heard of such a thing, indeed, headaches and diabetes do not go together. Diabetic patients practically never have migraineous attacks."

"**Pelvic headaches**"—We have been told much of pelvic headaches. A gynecologist of wide experience said, "There is no headache that may consistently be regarded as an ovarian or a uterine headache. Headaches are common during the menstrual period, but we can hardly call this a menstrual headache, since intermenstrual headaches of the same type too often occur in the same individuals." Dercum said, "Indeed, I think it may well be doubted whether a headache directly dependent on an uncomplicated pelvic disease really exists."

**Reflex headaches**—In regard to reflex headaches, von Leube says, "Very many clinical observations are still necessary to determine precise diagnostic points of support in this respect." That referred pain may result from diseased structures elsewhere, as in dental disorders, is well known.

**Sympathetic headache**—Of sympathetic headache it is said, "Sympathetic headache may supervene on disease of almost all the peripheral organs. The most common form of this variety is the brow ache of gastric catarrh." Sympathetic headaches, too, may be cast into the limbo.

**Gastro-intestinal headaches**—In differentiating migraine-like attacks from hyperacidity, Auerbach says, "Confusion may be avoided by remembering that migraine begins in childhood or adolescence at a time when hyperacidity is hardly seen." This differentiation would seem to provide very insecure footing, inasmuch as there are many exceptions to the rule that migraine begins early in life. We are advised elsewhere that an examination of the heart, urine, blood, eyes, sinuses, and reflexes is essential before a diagnosis of gastric

headache can be made. A diagnosis that hinges too much on exclusion also hangs by a tenuous thread. A review of the histories of cases of gastric headache shows that they resemble migraine, and the fact that the headaches are relieved by a careful regimen is also characteristic of migraine. No doubt intestinal upsets may produce migrainous attacks. Alvarez regards these disturbances as mechanical in origin, and related to distention of the rectum rather than to toxic factors.

#### ILLUSTRATIVE CASE

**Case 6** — A school teacher, fifty-one years of age, had had since childhood intense attacks of migraine every two weeks, and lasting one and one-half days. She was entirely well and actively engaged in work between the attacks. She had learned that resection of the colon might relieve the condition, and requested that this operation be done, standing ready to accept every responsibility. With a good deal of misgiving an iliosigmoidostomy, developed by Sistrunk, was performed. Six and a half months have passed since the operation, and for the first time since childhood this woman has experienced complete relief from the prostrating headaches. It remains to be seen whether the relief will be permanent.

It is well known that migrainous attacks often cease following cholecystectomy, yet there are too many exceptions to suggest this as a therapeutic measure. The profound effect that this operation may have on digestion is suggested by the researches of Mann.

Hare observes that 2,000 migrainous persons who had enteric fever did not, thereafter, have migraine, thus emphasizes the extraordinary and singular behavior of the disorder.

Bowing has noted that x-ray and radium treatment often produce headaches in patients who have hitherto been subject to headaches, but does not do so in other patients. This is true, regardless of the structures radiated.

All this leads to the inference that an unlimited number of factors, such as diet, constipation, exposure to wind or light, riding, eye-strain, worry, excitement, or late Sunday morning sleep may precipitate headaches in certain persons, whereas the same conditions do not have such a result in others. Therefore, in the treatment of migraine, we must reduce all sources of irritation and irregularity to a minimum.

The following cases are illustrative of this condition, and present some of the less usual features occasionally noted

**Case 7 Hemiplegic migraine and neurosis**—A woman, forty-seven years of age, came to the Clinic in November, 1922, because of fatigue. She had had no children. The right ovary had been removed in 1916, and a panhysterectomy performed in 1919. The patient had never been strong, but since the operation had complained of hot flashes, lassitude, backache, poor sleep, rapid fatigue, palpitation, and dyspnea on exertion. Between ten and forty-one years of age, she had had attacks of the following character once or twice a month. First there was a feeling of well-being, energy, and activity, the following day, scintillating scotomas, blindness, severe headache, nausea, and vomiting developed, next followed a sensation of numbness, which started in one extremity and involved the entire right or left side, and at times was accompanied by loss of speech. During the attack of numbness, which lasted one-half hour and subsided gradually, the side involved would become weak and clumsy, causing difficulty in walking and in buttoning the clothes. There had never been a residue, and because of this the attacks caused the patient no alarm. A diagnosis was made of migraine associated with hemiplegic attacks and chronic nervous exhaustion.

**Case 8 Ophthalmoplegic migraine**—A farmer, aged twenty-six years, presented himself for examination in January, 1923, because of sick headaches and drooping of the left eyelid. He had been well until he was four or five years old, when sick headaches began. They occurred about once a month, were usually introduced by a chilly sensation accompanied by nausea, vomiting, and headache, which was severe and continuous, they lasted two or three days, and caused him to lie down in a quiet, darkened room. The pain included the entire forehead, but was particularly severe in the region of the left eye and ear. The first indication the patient had of trouble with his eye was at the age of seven years, when he experienced diplopia which continued for two or three days, following an attack of headache with vomiting. A photograph taken at the age of ten years revealed slight deviation outward of the left eye. At the age of eleven years, a slight transitory ptosis of the left lid of two to three days' duration accompanied each attack of headache. The recovery was not always complete before the next headache set in, and at seventeen years of age the lid remained half way down. His grandmother and a cousin four years of age "get bilious attacks with headaches," and the mother was worried lest this cousin might also develop drooping of the lid.

Examination revealed a complete internal and external left third nerve paralysis, but was otherwise negative. Necropsy in this case might provide unexpected findings.

Some time ago I had the opportunity of observing a woman in an attack of migraine during which the left pupil became completely fixed to light and to accommodation, this was

on the side of the headache. The immobile pupil disappeared within two days, simultaneously with the disappearance of the headache, the pupil passing through the stage of an Argyll Robertson reaction on its way to complete restitution. The patient said that the pupil seemed to change with each attack of headache.

**Case 9 Abdominal migraine** — A woman, aged twenty-eight years, came to the Clinic because of attacks of abdominal pain. At the age of twelve years she began having black spots before the eyes for five minutes; blindness followed for three-quarters of an hour and aphasia for three and three-quarters hours. Intense headache persisted for from two to four hours, and was followed by abdominal pain for from four to five hours, at times so intense as to require morphin for relief, and a continuation of vomiting without pain for three or four days. At the end of the attack, a watery evacuation of the bowels occurred. The headache stopped when the patient was seventeen, but the abdominal attacks continued as before. When she was twenty-four, an appendectomy was performed without relief. Four years later, an abdominal exploration revealed no lesions. The family history was negative. Detailed examination, including full investigation for syphilis, was negative.

The headache of migraine may be dull or sharp, some one spot may be particularly painful, such as above the eye, the eye-ball itself, or the temple, but the pain may include the entire head. It is worse on jarring, as in walking, turning the head, or stooping and is aggravated by light and noise. Relief usually follows lying down in a darkened quiet room, and the pain usually does not interfere seriously with sleep. The headache may be fully as painful and quite indistinguishable from that occurring in brain tumor, however, in migraine the preceding elation, the attending excessive mental depression and lassitude, the scotoma, the shifting location of the pain in different attacks, the history of recurrent attacks over a period of years with complete freedom as a rule in the interim, and the objective examination, usually permit differentiation. As a rule the patient is quite familiar with its manifestations, and can readily distinguish these headaches from headaches of other origin. Tetany, possibly related to vomiting and all glossis, epilepsy, and hysterical embellishments, may produce an

extraordinarily complex syndrome I have never noted a slow or irregular pulse during an attack of migraine

That nocturnal migraine may occur is indicated by an interesting contribution of Feres in which he reports two cases of hemianopic scotoma occurring during sleep. In one case the patient dreamed that he saw fire and volcanic explosions, always on the same side, in the other case, a figure clad in white entered the same field of vision. On awakening, a typical migraine was present.

#### PSYCHONEUROTIC, PSYCHOTIC, NEURASTHENIC, AND EXHAUSTION HEADACHES

The headaches of psychoneurotic persons are not uncommon. Often they are associated with physical trauma, as in the following case.

**Case 10 Posttraumatic, psychoneurotic headache**—A man, aged twenty-four years, came to the Clinic in March, 1924, complaining of headache and loss of memory for six months. Six months before, he had been struck in the right frontoparietal area by a 10 pound weight. Further inquiry disclosed the fact that the weight was shaped somewhat like a window weight, and was attached to a cord that was pulled to move an elevator. He thought little of the accident, but one week thereafter a dull pain appeared in the injured region, and continued during all of his waking hours. It was relieved by rest, and was aggravated by work. During the last few months, mental confusion had attended efforts to think, and he said that he stammered and couldn't say what he wished to say. He was afraid of insanity, was nervous and irritable, and at times his whole body would quiver.

Physical examination was negative throughout. The patient had worked as foreman for an ice-cream company for three years, and had recently been transferred to less desirable work. In the course of discussing his work, he remarked that he had not had a vacation for three years, he referred to his boss as a "stingy bastard," and said, "I know him like a book." The patient claimed that he earned more than \$100 a month, but did not get it, and said that ice-cream work got on his nerves. He referred to his working place as a "damned hole," yet he was drawing compensation.

The headache was regarded as an evidence of psychoneurosis, malingering, or both. The patient was obviously disgruntled and dissatisfied. It was suggested that he change his work, since he had no further advancement in sight, and the matter of vacations was discussed with him.

Hurst says that persistent headache due to concussion, whether caused by direct injury or a shell explosion, is often,

if not always, of an hysterical nature, as it disappears with psychotherapy. Doubtless this is often true, however, it would seem difficult to prove that every case of posttraumatic headache is due to hysteria.

The trauma producing headache need not be physical. As Jellisse says of headache, "It is one of the universal scapegoats for meliorizing psychologic conflicts." This factor is doubtless responsible for the complete disability in the following case.

**Case 11 Head pains in a psychoneurotic patient.**—A woman, aged twenty-five years, came to the Clinic in October, 1924, for a "general examination." She complained of being very nervous, said that her face was paralyzed, and hurt, and that she had intensely painful menstruation. Four years before, pain had developed in the right lower first molar, and a dentist had filled the tooth. On the following day, a complete right-sided facial paralysis developed. The patient was told that the paralysis would clear up after three months, but when it failed to do so, she went to another dentist, who removed the tooth and some loose bone, and at the same sitting broke into the right antrum, which he kept open for two months. The facial paralysis gradually improved, but the patient began to complain of flesh quivering in her side and feet, and jerking of the legs, which consisted of a coarse tremor lasting ten or fifteen minutes, and came on particularly when she was touched. The first time it appeared when her mother inadvertently touched her while she was sleeping, she said, "I hate to have anyone touch me." She admitted that her feelings were very easily injured, thus on her suggestion that they get a morning paper, she became greatly disturbed because her mother remarked that they would not have time to read it. The pain in the right side of her head and face was often extreme, particularly at the menstrual time, when it would extend down the right arm and include the right breast. At first she denied any sensitiveness regarding the facial palsy, but later said that everyone looked at her, and that it caused her much concern.

Examination disclosed a faint systolic murmur, some retroversion of the uterus, absent molars on the right side, and the residue of a right facial palsy. The complaints and the marked emotional reaction were not adequately explained from a physical basis. On further questioning she divulged the following. Four months before the teeth were extracted and the facial palsy appeared, she was told by the man to whom she was engaged that he was responsible for pregnancy in another woman, and that he did not know what the outcome would be. He disappeared on that day, and the patient had not heard from him since. She cried when this subject was touched, but both the mother and the patient assured me quickly and very characteristically, that the matter had been entirely dismissed from her mind.

In this case minor complaints were tremendously magnified to serve as a retreat from a still more painful situation. Parker has recently contributed an illuminating article on pain in the fifth nerve area, in which he discusses the differential diagnosis. Case 11 is similar. Here we evidently have a combination of migraine and a psychoneurotic headache.

Case 12.—A student, aged eighteen years, was brought to the Clinic by her mother in August, because of frontal headaches. The headaches began about seven years before, when the patient was eleven years of age, they were frontal, of a "dull pressure" type, not aggravated by shaking the head or stooping, they came on once or twice a week, especially after quarreling with a younger sister. One and one-half years before examination, these headaches had become more marked, and she had to give up her school work because of them. She consulted various doctors, and several operations were performed on the nose, teeth and tonsils, without relief. One month before she came to the Clinic, the headache extended to the vertex. Inasmuch as she had obtained no relief from the other measures, a decompression operation was performed. There seemed to have been some difference of opinion among the physicians. The operation was followed by relief from pain for four months, the headaches then returned with renewed vigor, grew steadily more intense, and became almost continuous. Further nasal surgery was advised. The patient was under the impression that she had a deep-seated tumor, and that it was largely a matter of temporary relief. In spite of the exquisite pain, she was able to sleep well at night, and could go almost anywhere she pleased. She went to parties where no one knew how much she suffered, so well could she conceal her discomfort. The patient was made much of by parents and friends, she was regarded as a brilliant individual with a great future before her, and hoped to take up Chautauqua work as a public speaker. While she was greatly interested in public speaking, she was not altogether pleased with the woman teaching this subject. At home she would say, "I can't stand Miss E any more, I wish I could throw my book at her." Other teachers also irritated her, but Miss E was the only one who criticized her, and whose "sight she hated." In May, 1923, the patient gave a recital and thought that she had completed her work in this course. In September, however, she again took up public speaking, at the behest of her father, but much against her will. She was very eager to get first honors, and competition was not always easy for her. On special occasions she became very much excited, danced and talked, but after the event, she would be prostrated. She often spat out to her mother, "O, why do you ask me how I feel, you know I cannot get well." She had the reputation of complaining very little, but of suffering greatly.

The mother formerly had had left supra-orbital "neuralgia," which often came on during the menopause, and was sometimes associated with vomiting. Until two years ago, she had been very excitable, cross, and cried easily. She

was agitated in her speech and manner, talked rapidly and at length, but seldom to the point.

The patient herself looked like a fifteen-year old girl, she walked lightly, and spoke in a jovial manner, was intelligent, interesting, alert, and evidently high strung. The general examination was negative throughout, save for evidence of a decompression operation.

**Psychotic headaches**—In the psychoses particularly those associated with depression, patients often complain of a dull, aching headache. This may be the chief complaint, and unless one is curious enough to inquire into the emotional life of the patient, the real basis may be overlooked.

**Neurasthenic headaches**—This type of headache is similar to the psychotic type. It is usually a sensation of pressure, or of a tight cap, rather than of pain. Whether it is psychogenic, somatogenic, metabolic, hereditary and an expression of biologic inferiority, or otherwise, does not seem to be known. It would seem that there are persons who were "born tired". Faulty education and unconscious imitation may be a factor, yet it would be arbitrary to assert that this condition is always entirely psychogenic. Some of these persons are ambitious, and interested in their work, they may actually accomplish a great deal, for which they receive good compensation.

**Exhaustion headaches**—Headache closely resembling the neurasthenic type may follow prolonged and extremely arduous mental application. This may be seen occasionally in school children, summer school students, attorneys, and ministers who work prodigiously for long hours and get little sleep. Such headaches bear a definite and reasonable relationship to the amount of exhaustion, and disappear quickly on rest, thus differing from neurasthenic headaches which are developed out of all proportion to the amount of actual exertion.

#### THE NEURALGIAS

Most of the classifications of neuralgia are dilapidated remnants of the bicker physiology. If the word "neuralgia" is to be retained and there is need of such a word, it should mean something. Among the causes of neuralgia we find listed

cancer of the liver, caries of the vertebra, and cancer of the pleura. In one of the best modern textbooks appears the statement, "A neuralgia may be due to carcinoma of the breast." Why not examine the patient and replace the empty gesture "neuralgia" by the word pain, or by a diagnosis of tuberculosis of the spine or cancer of the breast? The better the examination, the fewer the intercostal neuralgias one sees, indeed, the better the physician, the smaller his experience with this rare condition.

There is a well recognized, sharply circumscribed clinical syndrome, not accompanied by any demonstrable pathologic changes in spite of years of duration, that may be chosen as the nucleus around which to erect the concept of neuralgia, this entity is trifacial neuralgia. Here we have a well-defined affliction whose outstanding manifestation is a flashing pain, limited exactly to the distribution of the fifth nerve or its branches, usually severe, spontaneous in appearance, often precipitated by talking and by chewing, without objective findings in the free interval. Confusion with other types of pain in the face is hardly possible. Exactly the same syndrome, but limited to other nerves, is seen in (1) glossopharyngeal neuralgia (Doyle) with its pain flashing between the tonsil and the region of the ear, and its trigger point in the tonsil, and (2) the type of occipital neuralgia which has a pain analogous to that of trifacial neuralgia.

The word neuralgia is often applied to post-herpetic discomforts, here the pain is more often a continuous, burning sensation which appears at the site of the eruption. The pain may last for years, and is particularly distressing when occurring in elderly persons. The word neuralgic is often used to qualify those attacks of migraine in which the pain may radiate, as to the face. Alcohol injections have often been given to relieve this pain, but with no success.

#### SUMMARY

In studying a case of headache, it is important to obtain a careful history. Seven points, at least should be ascertained.

(1) location of pain, (2) duration, (3) frequency, (4) character, (5) intensity, (6) course, and (7) associated symptoms and relation to other functions

Careful and complete examination is indicated. It should be determined, if possible, whether the headache is the expression of (1) organic disease involving structures of the head, in this connection the aid of the ophthalmoscope should never be neglected, if brain tumor is a possibility, the pulse should be noted carefully for slowing in rate and irregularity, and the occurrence of precipitate vomiting inquired into, the organs of special sense call for investigation, and the skull should be palpated, and an x-ray examination made, (2) toxic factors, especially nephritis, (3) circulatory disturbances, especially hypertension, (4) migraine and its variations, here we are dealing with the patient rather than with the cause, (5) psychoses, psychoneuroses, neurasthenia, and exhaustion, the emotional behavior and daily habits of the patient should be ascertained, and (6) neuralgias; not every pain is neuralgia

Combinations of the foregoing conditions are possible. Certain cases may require prolonged observation before a diagnosis can be established

## RECURRING EPILEPTIFORM ATTACKS WITH SYM- TOMS OF SPASM AT THE CARDIA. REPORT OF THREE CASES

ANDREW B RIVERS AND WINFRED H BUEERMANN

**Case 1**—A physician, aged forty-nine years, had noticed for the last three years slight gastric discomfort associated with periodic attacks of pyrosis, due to dietary indiscretions. For three months before coming to the Clinic he had noticed a suggestion of dysphagia, about once or twice in two weeks, which lasted not more than a minute, and was more marked after the ingestion of dry food. During the course of one meal he had two spells of dysphagia, they were not associated with dizziness, paleness, coughing, or regurgitation of food. Five weeks before coming to the Clinic, while at breakfast, he had a spell of dysphagia, food seemed to stick below the sternum. Syncope followed for about thirty seconds, during which time the patient became unconscious, and pale, and he fell forward relaxed, on the table. There was no twitching of muscles or convulsive contractures. Immediately on the return of consciousness he felt quite normal, with no residual weakness or drowsiness. He had no premonitory symptoms except the dysphagia, he said that he felt as though a drink of water would have given prompt relief. The following week, while eating luncheon, he had a similar attack of syncope, preceded by dysphagia, lasting about thirty seconds, with complete loss of consciousness. He later returned to consciousness and had no residual drowsiness. The following week, at breakfast, he had another similar attack. After each attack the patient was able to finish his meal as though nothing had happened. For two weeks before coming to the Clinic he was free from the attacks. His appetite was good, and bowel movements were regular, but he lived in constant fear of having an attack of dysphagia with syncope while eating in a public place.

General examination revealed a normal condition of the fields, reflexes, fundi and pupils, except that the latter were slightly irregular. The chest was normal in contour, the movements were symmetric and the lungs resonant and clear. The heart was normal in size, the sounds were regular, but there was a reduplication of first sounds at the apex and base, without murmurs, the aortic second sound being accentuated and snappy. The abdomen was slightly obese, without palpable masses or areas of tenderness. The rectal examination was negative. The systolic blood pressure was 130, the diastolic 95, the pulse rate 72, and respiration 98. There were no lesions in the nasopharynx or larynx. The urinalysis was negative, the hemoglobin was 80 per cent (Dare), the leukocytes numbered 7,600, the total acidity was

30, and the free hydrochloric acid 10, with 260 c.c. of secretion, and normal chymification. The Wissermann reaction was negative. Roentgenograms of the mouth revealed periapical infection in three teeth, those of the chest calcified glands at the hilus, but those of the stomach were negative, although on fluoroscopy a lagging was noted at the cardia. Electrocardiographic tracings demonstrated a rate of 64, with sinus bradycardia and a left ventricular preponderance. A thorough neurologic examination failed to reveal any changes in the central nervous system. A sound was passed into the stomach with ease, and no discomfort to the patient. The cardia dilated with a hydrostatic dilator to 24 of water pressure, which caused rather marked epigastric pain temporarily. On the patient's second visit to the Clinic a definite cardiospasm was easily dilated.

**Case 2**—A man, aged fifty-nine years, came to the Clinic mainly because of dysphagia and syncope. In 1910 he first noticed dysphagia at one of his meals, but he does not remember the type of food eaten. Between 1910 and 1920 he had four such spells, they lasted only a few moments, but all were severe enough to make him remember the incidents distinctly. During the spring of 1920, while at dinner, he had had a feeling that food was sticking in his esophagus, and that his air passage was occluded as he had great difficulty in breathing. After a few seconds he lost consciousness and fell from his chair to the floor. Before his mother, sitting across from him, could get to him he had regained consciousness. He got up unaided, and finished his meal. There were no associated convulsions, no weakness after the attack, no drowsiness, no injury during the fall, and no sphincter relaxation. The only premonitory warning was difficulty in breathing. One month later he had another similar attack of dysphagia. This time he arose from the table and walked about five steps before he lost consciousness and dropped to the floor, where he lay quietly for several seconds, then stood up unaided. He said that when he regained consciousness he "felt like a fellow coming from the other world." Between the time of his first and second epileptiform seizures he had three attacks of dysphagia while eating dry food, but these were not associated with syncope and were only momentary. The dysphagia usually occurred after swallowing a small bolus of food. Since the second attack of syncope the patient has had about one attack of dysphagia a month, becoming weak and dizzy, but not losing consciousness. This patient also is in constant dread of attacks while dining in public. He has never regurgitated food, or vomited, his appetite has been good, and the bowels regular.

The patient weighed 182 pounds. The findings of the respiratory, cardiac and urinary tracts were negative objectively. The eyes reacted to light and accommodation, vision was normal, and examination of the reflexes, fields and fundi was negative. There was evidence of periapical infection in five teeth. The chest was large and barrel shaped, resonant throughout with distant breath sounds but no rales. The abdomen was slightly obese. There was a right scrotal hernia that was easily reducible.

The urinalysis was negative, the hemoglobin was 75 per cent, the erythrocytes numbered 4,140,000, the leukocytes 4,900. The Kolmer-Wissmann test was negative. Roentgenograms of the stomach, esophagus and chest were negative but on fluoroscopic examination a small mediastinal

shadow was seen on the right side in the upper mediastinum. An electrocardiographic tracing revealed a rate of 69, with a left ventricular preponderance and a diphasic T-wave in Lead III. A careful neurologic examination failed to disclose anything of importance, examination of the nasopharynx revealed large septic tonsils, absence of the uvula, and a polypoid enlargement of the left false cord, which probably accounted for the hoarseness which had existed for the last twenty years. A 41-F olive was passed into the stomach without meeting any obstruction.

Case 3.—A woman, aged fifty-one years, entered the Clinic complaining of headaches, gastric disturbances, intermittent pain below the sternum while swallowing, and rectal spasm. She had been married three times, the first husband died of meningitis and the second of locomotor ataxia (?), the third is living and well. The patient's father died of apoplexy, and her mother of carcinoma of the stomach. A history was elicited of influenza, malaria and headaches beginning at the birth of her first child. These were described as severe pains over the vertex and occiput, coming on periodically and lasting a day or two. They were not associated with vomiting, although the patient was slightly nauseated and felt generally ill. Two daughters had similar headaches. During the last two years the patient has had two attacks lasting several months, during which she had pain over the entire head, thumping and throbbing in character, and intensified with each heart beat. It has frequently been necessary to use codein to control the pain. In the interval between these spells the patient has had very little of her previous cephalgia. The gastric disturbances have been present for two years, and are quite characteristic of cholelithiasis. Three years before, while the patient was at the table, she suddenly lost consciousness for a few seconds, then continued her meal apparently none the worse for her unusual experience. There were no convulsions, and no involuntaries. She did not remember whether there was any substernal pain at this time, but frequently since then food seemed to stick in her throat, remaining in one spot for a few seconds, during which she had very severe substernal pains, and a sensation of choking. The pain persisted until she washed the food into the stomach. During the attack of pain the patient was usually weak and dizzy, and had a feeling that she was going to faint. A year later, while eating, she again noticed the sticking in her throat, the pain was extremely severe, she felt dizzy and very weak, but did not lose consciousness. She emphasized the fact that during this attack her pulse rate was very slow, about 40. A doctor was called immediately and on learning of the symptoms decided the patient might have angina, but she promptly regained her strength and composure, and was able to continue normally with her routine activities.

The patient was rather obese and nervous. There was moderate evidence of arteriosclerosis in the peripheral arteries. The systolic blood pressure was 110, the diastolic 80, the temperature 98.6°, and the pulse rate 80. The pupils were equal, reflexes normal, vision was 6/60 in the right eye and 6/6 in the left, the fundi were negative. There was some evidence of infection around the teeth. Examination of the nose and throat failed to show any definite lesions. There was tenderness over the area of the gallbladder, pelvic examination disclosed nothing of importance. The urinalysis on two

occasions was negative, the hemoglobin was 70 per cent (Dare). The erythrocytes numbered 4,700,000 and the leukocytes 3,900, the differential count was practically normal. Gastric analysis showed a total acidity of 40, free hydrochloric acid 20, and a total quantity of 85 c.c. The Wassermann reaction on the blood and spinal fluid was negative, as were also six provocative Wassermann tests. Roentgenograms of the sella turcica, gastro-intestinal tract, kidneys, ureters and bladder were negative. Electrocardiographic tracings showed a rate of 82, sinus rhythm, a left ventricular preponderance, and an inverted T-wave in Derivation III. Neurologic examination failed to reveal any organic changes in the central nervous system. Because of the negative x-ray findings, esophageal dilatation was not considered necessary.

### DISCUSSION

The somewhat unusual features in these cases were the incidence in persons past middle age, the youngest being forty-nine years old, the definite psychoneurotic personalities, actual obstruction at the cardia in only one case, and the onset of symptoms after the ingestion of solids rather than liquids. Immediately after attempting to swallow, a choking sensation developed, associated with severe substernal pain. This pain was well localized over the lower sternum, but occasionally radiated over the upper chest. The symptoms arose at any time during the course of the meal. Shortly after the onset of the pain, the patients lost consciousness. In a few instances marked weakness and dizziness preceded the loss of consciousness. There was no cyanosis, and no convulsions were noted. Sphincter control remained intact, and there was no evidence of injury to the tongue or lips. The return of consciousness was rapid, and there was no residual drowsiness. Immediately after the attack, the patients resumed their activities, as though nothing unusual had happened.

Although these three cases suggest the existence of a cardio-spasm, this was discovered in only one instance, after several x-ray examinations. The spasm seemed rather to be a temporary reflex at the cardia, with a lesion elsewhere in the digestive tract, or a spasm vagal in origin, with a functional or organic background. The similarity of these symptoms to those of so-called laryngeal epilepsy is interesting. The succession of events characterizing the two conditions can be thus represented:

Esophagus.	Trachea.
Choking sensation	Cough
Spasm at the cardia	Spasm of the glottis
Substernal pressure	Dyspnea
Syncope	Syncope
Slow pulse	Slow pulse
Rapid recovery	Rapid recovery

Douglas, in a recent contribution, says that laryngeal epilepsy is a state of unconsciousness produced by an epileptiform attack, originating from a laryngeal irritation, usually some form of laryngitis. He infers also that these symptoms are found in nervous persons past middle life who usually are free from "epileptic taint." He noted muscular relaxation during unconsciousness of the patient, although the usual signs of epileptic seizures seem to have been wanting. These findings are similar to those in the three cases reported here, in which convulsions were absent, and there were none of the stigmas or personality characteristics so often noted in epileptic persons. Our patients were also past middle life and extremely nervous.

Oppenheim quotes Kraus in the statement that symptoms like those of cardiac spasm are caused by lesions involving the vagus. In one of the cases reported, fluoroscopy revealed a mediastinal enlargement which may have involved the vagus. Vinson, in discussing the symptoms of cardiospasm, mentions irritative lesions involving the vagus as one of the etiologic factors. Loeper and Forestier reported a case of carcinoma of the lesser curvature which induced recurring spasms of the cardia. They assumed that "the cause was evidently the neuritic lesions found in the vagus and progressive and ascending cancerization of the fibers in the region of the cardia." Bing's description of vagal crises includes, first, changes in heart rate, notably a slowing, second, dyspnea, third, apnea, and fourth, loss of consciousness. Vagus stimulation according to a number of authors, may produce transitory heart-block. Councilman and Edes have described a group of neurotic patients with heart-block, the etiology of which they attribute to irritation of the vagus nerves. Hewlett says that stimulation of the vagus nerves frequently produces partial heart-block.

In susceptible persons partial block has been observed during the increased vagus activity that follows swallowing and during the slow heart action accompanying expiration. Willius describes the case of a young man with complete heart-block in whom no cardiac disease was demonstrable. He suggests the possibility of central vagal influences as an etiologic factor.

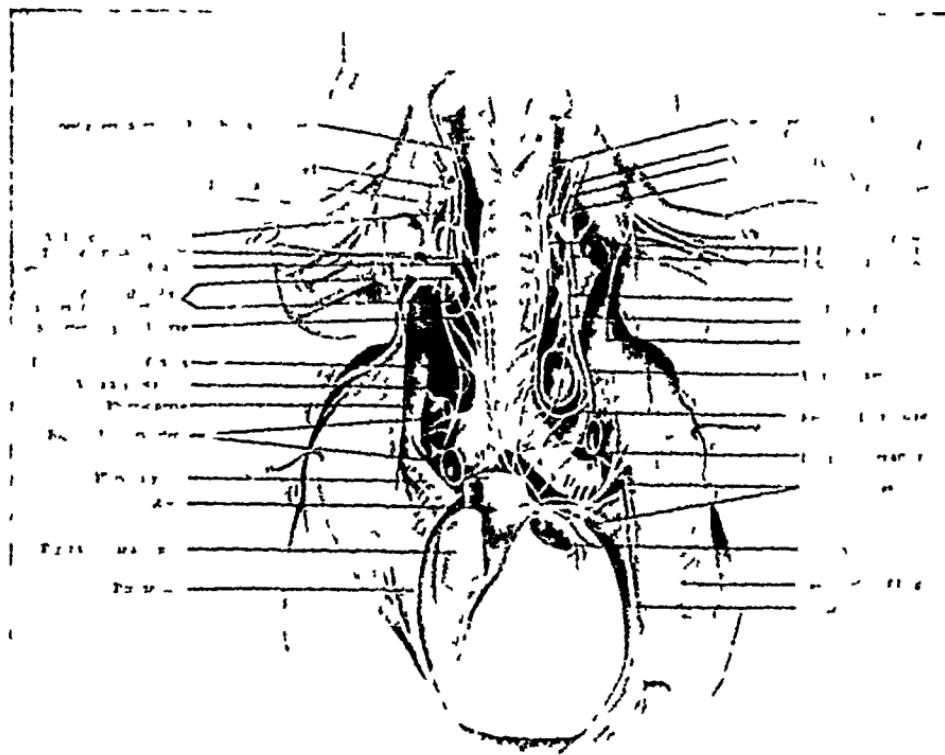


Fig. 221.—Dissection showing lower part of pneumogastric nerves and their branches (After Piersol.)

Iherms explains the phenomenon by assuming that an afferent impulse passes from the superior laryngeal to the pneumogastric nerve and thence to the respiratory center in the medulla, thus causing efferent impulses culminating in cough, dyspnea, and syncope. The older writers, notably Armstrong and Getchell, in discussing the possible etiology of the cases of laryngeal

epilepsy, consider lesions of the vagus as an etiologic factor

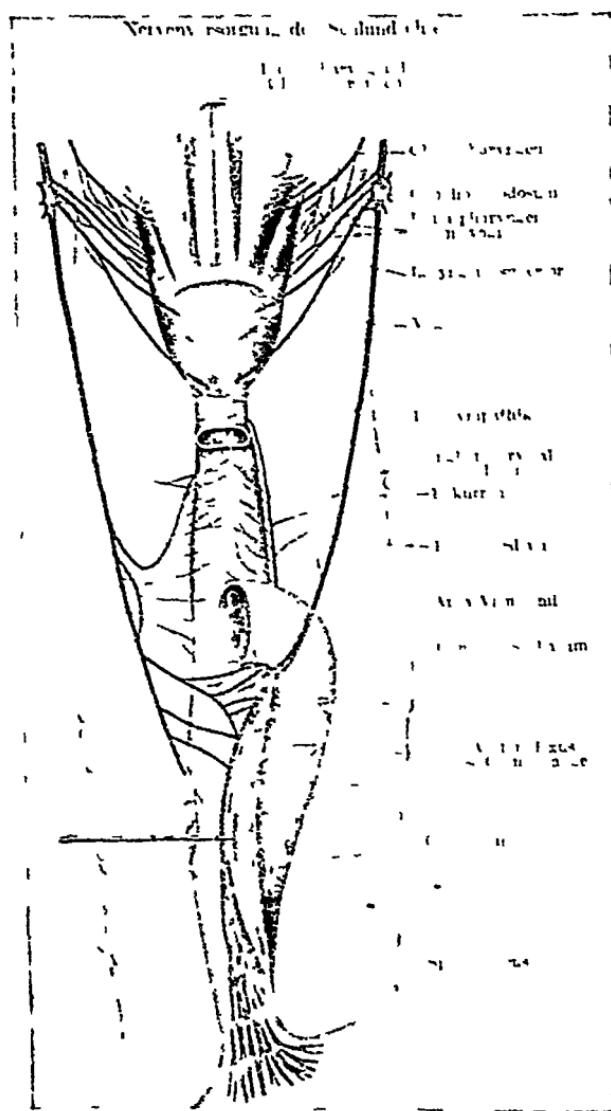


Fig. 222—Nerve supply of the pharynx and alimentary canal (After Greving)

Getchell includes the following in his final remarks "The spasmodic closing of the glottis may, and in many cases does,

act directly and immediately upon the inhibitory centers of the brain and cause syncope

"A severe paroxysm of coughing which produces congestion of the cerebral vessels may also cause syncope. But it will not cause it unless there be an exciting disorder of the central



Fig 223.—Dissection showing cardiac branches of pneumogastric nerves and of sympathetic cords, aortic arch and branches and pulmonary artery partially removed, pericardium laid open (After Piersol.)

nervous organ." The phenomena under consideration occur in persons in whom there is evidence of an unstable equilibrium of the central nervous system

There are several ways in which one might attempt to explain these symptoms. We may be dealing with a condition which might be termed "esophageal" epilepsy. The spasm at the cardia could then be part of the aura. Another interesting

postulation would be to assume vagal irritation, because of this spasm at the cardia, dyspnea, bradycardia and loss of consciousness, a condition resembling the neurotic type of Stokes-Adams syndrome

Figures 221-223 show the relationship of the sympathetic and vagus nerves to the esophagus and trachea. The nerve supply to the esophagus is derived for the most part from the vagi, but it also receives fibers from the sympathetic. These form a plexus on the anterior cardiac portion of the esophagus which sends fibers to both coats, the muscular and the mucous membrane.



## THE KETOGENIC DIET IN THE TREATMENT OF EPILEPSY. REPORT OF TWO CASES

M G PETERMAN

I wish to present two patients with epilepsy who have been treated with the ketogenic diet

Case 1 — This boy, aged nine and a half years, had had epilepsy, grand mal, for one year previous to registration at the Mayo Clinic. He was having from one to ten attacks a day, and each attack lasted for from three to twenty minutes. The boy's father had migraine. There was nothing of importance in the history, and the physical examination was essentially negative. The blood Wassermann test was negative, as were the roentgenograms of the skull, and examination of the fundi.

The boy was put on a starvation diet consisting of from three to five oranges a day and water, for one week. He was then put on a ketogenic diet. There were no convulsions for three months. Then, following an indiscretion in diet, there was a grand mal attack. The patient was again well for two months when a break in the diet occasioned a second attack. Ten months later a third seizure followed a break in diet. From this time on the patient was free from attacks, and during the entire period of treatment he had been well, and had gained in weight normally. Six months after the last attack the boy's father, a physician, wrote that his condition was excellent, that "the boy is the brightest he has ever been, and is at the head of his class." The father then placed the patient on a general diet. No further attacks have occurred.

Case 2 — A boy, aged nine years, had had epilepsy, petit mal, for three years. The disease had progressed gradually, and on his admission to the Mayo Clinic the attacks, which lasted from one to three seconds, occurred about twelve times a day. The boy was placed on the Ketogenic diet September 14, 1923. He had three attacks of petit mal during the first fourteen days of treatment, but none since. After two months the diet was gradually modified, the carbohydrate was increased and the fat decreased. The patient then remained on a 2:1 (K/A K Shaffer) ratio for five months. He is now on a general, full diet and is entirely free from attacks.

These two cases, of one and three years' standing respectively, illustrate the results obtained with the ketogenic diet in the treatment of epilepsy. A case of eleven years' standing has been

successfully treated in the Clinic. However, no attempt has been made to treat patients with manifest mental degeneration, in whom the degenerative changes can hardly be influenced by dietary measures. The most striking results have been obtained in cases of petit mal, a form of epilepsy which does not respond well to luminal. Several patients who did not respond immediately to the ketogenic diet, did very well after a week of starvation. It is the object of the ketogenic, or high fat, diet to produce a ketonemia. The patients are kept in this state of ketosis at least during the first few months of the treatment. No harmful results have been observed.

The ketogenic diet is not started abruptly. The patient is given a diet of carbohydrate 50 gm, protein 25 gm, and fat 70 gm, for one or two days. He is then given carbohydrate 40 gm, protein 20 gm, and fat 80 gm. Following this, on the fourth or fifth day, the diet is modified to carbohydrate 20 gm, protein 20 to 30 gm, and fat 92 gm. If there has been no nausea or emesis, the patient is then put on his full diet prescription, which consists of 10 to 15 gm of carbohydrate a day, 1 gm of protein for each kilogram of body weight, and fat for the remaining calories. (Excessively obese patients require special consideration.) The total caloric intake should not exceed the actual metabolic requirements. The caloric requirement is easily calculated from Wilder's chart. Thirty to 50 per cent is added to the basal metabolic requirement. Provision is made for the vitamins and salt.

## THE VALUE OF DEFINITE METHODS OF TREATMENT OF MALIGNANT AND NONMALIGNANT CONDITIONS

HARRY H BOWING AND J HERBERT BLISS

By employing a standard technic in the management of definite cases in which radiotherapy is indicated, we can now predict with reasonable certainty the possible response in a given case. If failure occurs, we must look elsewhere for the cause of the faulty result rather than to the therapeutic method employed, as illustrated by Cases 1, 2, 3, and 4. Cases 5 to 10 demonstrate the value of radiotherapeutic methods in the treatment of malignant disease.

Case 1.—A woman, aged thirty-five years, came to the Clinic May 24, 1920, complaining of profuse menstruation. Her father and one sister had died of tuberculosis (?) She had had measles, and mumps in childhood, pleurisy (?) occasionally, frequent "sore throat attacks," and typhoid fever. She had been married fourteen years, but had only one child. In 1915 an adenoma of the left lobe of the thyroid (non-toxic) had been enucleated. Sixteen months before coming to the Clinic, the patient had a prolonged but otherwise normal delivery of a healthy full term child. Five months post-partum menstruation returned, it was very profuse, contained clots, and lasted ten days. Following childbirth she noticed a swelling of the neck, and she thought that the goiter was returning. Her general strength had been poor since childbirth. She became fatigued readily and had little ambition or energy. Her appetite had been poor but she had forced herself to drink 2 quarts of milk daily.

On examination the patient weighed 123 pounds, her height being 5 feet, 8 inches. There was moderate dental sepsis, but otherwise the general examination was essentially negative. The systolic blood pressure was 130 and the diastolic 70, pulse rate 104, and temperature 99°. Urinalysis showed a trace of albumin. The hemoglobin was 80 per cent, the erythrocytes numbered 4,610,000, the leukocytes 8,800. The blood Wassermann reaction was negative. x-Ray examination of the chest was negative. Stool examinations revealed no ova or parasites.

A diagnosis was made of menorrhagia (etiology questionable), and chronic nervous exhaustion. A small dose of intra-uterine radium was recommended, and May 31, 1920, the patient received 30 mc. of radium, intra-uterine, for

twelve hours. Following this, she had amenorrhea for ten weeks, then a normal flow for eighteen months, but during the year from June, 1923, to June, 1924, she thought the flow was twice the normal amount. September 12, she returned to the Clinic, complaining of being "weak and run down," although for three months she had had practically normal menstruation. The systolic blood pressure was 130, the diastolic 80, the pulse rate 84, and the temperature 98°. The thyroid was palpable only, the lungs were clear. Pelvic examination revealed that the cervix was lacerated bilaterally, and that the uterus was slightly enlarged, and probably contained a small fibromyoma. Urinalysis revealed a low specific gravity (1.009), acid reaction, a trace of albumin, no sugar, and few pus cells. The hemoglobin was 83 per cent, the erythrocytes numbered 5,380,000, and the leukocytes 10,000. The blood Wassermann reaction was negative. According to the x-ray there was dental sepsis, and the chest was negative. Several basal metabolic rates were taken, two, reported before thyroid extract was given, were -8 and -15.

It was thought advisable to bring the low basal metabolic rates up to normal before attempting the use of more radium for the menorrhagia. Accordingly, the patient was given thyroid extract, 4 grains four times a day for four days, and 2 grains four times a day thereafter. Subsequent observations showed the basal metabolic rates to range from +3 to +7. On dismissal October 13, 1924, she was instructed to continue the thyroid extract, 2 grains four times a day, for six months, when she was to report again.

*Comment*—It is our policy to be ultra-conservative in the use of radium in treating menorrhagia in young women. The small doses, repeated from time to time if necessary, are very efficient in the majority of cases. In this instance the result was fairly satisfactory, but the patient failed to regain her strength and felt generally "run down" although she volunteered the statement that she felt her best during a period of amenorrhea following the radium treatment. This statement could easily lead to the conclusion that a therapeutic menopause was indicated. During a careful physical examination, she was found to have a low metabolic rate, this was checked and treatment instituted to establish a normal rate, and in all likelihood she will regain her strength as soon as the rate is normal. Further radium treatment was not recommended at this time.

**Case 2**—A woman, aged fifty-one years, registered at the Clinic April 30, 1923, complaining of persistent uterine bleeding. On two previous visits, in 1909 and 1910, there was no evidence of this trouble. Her previous illnesses included scarlatina, typhoid fever, rheumatic fever, and bronchopneumonia several times. Menstruation had been normal until the present illness. Curettage had been performed in 1913. She had been married

seventeen years without children, but had had two miscarriages fifteen years before examination, following which her doctor said she had had "Bright's disease" and "hypertension." Ten years before, the patient first noticed prolonged menstrual bleeding daily which lasted nearly three months. Curettage did not bring relief. She was then sent to bed on a milk diet, with temporary relief from the flow for five weeks. In April, 1920, radium was inserted into the uterus, with cessation of menstruation for one year, only to be followed by a more profuse flow. Radium was again inserted in September, 1922, but again with only temporary relief, and for five weeks preceding examination the flow continued daily. Leukorrhea, odor to the discharge, or associated pain had not been noted.

She had had some dyspnea on exertion for ten years and said her heart beat was rapid but regular. She "took cold" readily, she had had nocturia from two to four times each night since childhood. Three years before, with a profuse uterine hemorrhage, she had been unconscious intermittently for ten days, and could not see during this period. For the last three years she had complained of numbness of the fingers, which had become progressively worse.

Examination showed that the patient was rather markedly obese, weighing 178 pounds, and quite pale. Her blood pressure on admission was 210 systolic and 104 diastolic. Three days later it was 175 systolic and 95 diastolic. Her temperature was 99°, and pulse rate 84. A moderate degree of peripheral arteriosclerosis was present and the eye-grounds showed some retinal arteriosclerosis, especially in the right eye, with some edema of the right optic disc. There was moderate dental sepsis, and the tonsils were fibrous. Cardiac examination showed a systolic murmur over the entire precordia, with accentuation of the aortic second sound.  $\alpha$ -Ray examination of the chest revealed cardiac enlargement 2. Pelvic examination revealed that the cervix was short, soft, and exposed with difficulty, and that the fundus was regular and smooth in outline, but about 14 cm in diameter. Urinalysis of a catheterized specimen of urine revealed a trace of albumin, a few hyaline casts, and a few red blood cells and pus cells. The renal functional test was 30 per cent (intravenous). The blood urea was 38 mg. The hemoglobin was 76 per cent, the erythrocytes numbered 4,280,000, and the leukocytes 16,400, with 95 per cent polymorphonuclear cells. The coagulation and bleeding times were normal on the first occasion although the coagulation time a few days later was nine minutes, with a calcium time of fifteen minutes. The blood Wassermann reaction was negative. The electrocardiographic report disclosed an aberrant QRS in Derivations I and II, notched P wave in Derivation I, and inverted T in Derivations I, II and III.

A diagnosis was made of obesity, hypertension, myocardial degeneration and metrorrhagia, probably due to uterine fibromyomas. Radium treatment was advised to control the metrorrhagia, as malignancy of the uterus was thought improbable because there was no suggestive history. Curettage was prevented by the cardiovascular-renal condition at that time. On May 3, 1923, the patient received 100 mg of radium for twelve hours, and was dismissed May 9 to report by letter in six months. She returned August 20. There had been some bleeding and considerable foul smelling leukorrhea.

with blood, following the radium treatment. The blood pressure was 220 systolic, and 110 diastolic, on two successive days. Pelvic examination revealed that the cervix was atrophic, the uterus seemed slightly smaller and was freely movable. There was a slightly blood-stained vaginal discharge. The hemoglobin was 80 per cent, the erythrocytes numbered 3,140,000, and the leukocytes 9,000. Urinalysis revealed the same findings as the previous examination. The bloody vaginal discharge was thought to be partly a post-radium reaction, and possibly due partly to hypertension. The patient was dismissed with the advice to continue dieting and limiting her activities.

Approximately ten months after the radium treatment, the patient returned to the Clinic. She had had a severe uterine hemorrhage to the point of exsanguination, and requiring vaginal packing to control it, five months before. Menstruation then seemed normal for two months, but subsequently the bleeding had been more or less continuous, requiring from one to five napkins daily. Likewise, she had had menopausal symptoms for the last five months. Her weight was not reduced, but anemia was evident from her pallor. The blood pressure was even higher than on prior examinations, 230 systolic and 140 diastolic. The uterus was four times the normal size, irregular in shape, and firm, but in its normal position and freely movable. There was no free bleeding at the time of examination. Otherwise there was no change in the findings.

The patient was sent to the hospital for medical treatment for her hypertension, her renal functional test was 16 per cent. The blood urea was 28 mg, creatinin 1.5 mg, uric acid 3.2 mg, the hemoglobin was 85 per cent with 5,360,000 erythrocytes and 13,000 leukocytes, and 77.5 per cent of polymorphonuclear cells. After ten days' rest, her weight was reduced to 165.5 pounds and her blood pressure to 180 systolic and 90 diastolic. After surgical consultation, a curettage was considered inadvisable, in view of the history and physical findings, and more radium treatment was instituted. Two vaginal applications of radium (100 mg for fourteen hours) were used, combined with topical applications over the lower abdomen of 5,500 mg hours extending over a period of four days. On February 28, 1921, the patient complained of an irregular heart action which she had had intermittently for several years. Examination at this time showed myocardial degeneration with hypertension and paroxysmal auricular fibrillation, for which tincture of digitalis was given with full physiologic effect. She was dismissed much improved March 1.

*Comment.*—This case is typical of a small group of cases in which menorrhagia seems to play a double rôle. It usually signifies uterine fibromyomas, as was substantiated in this case by a bimannual examination, and it is possibly a factor in preventing the usual rupture in the arterial tree, which would result in paralysis and probably death. The technic as applied in the first treatment gives a high percentage of favorable results, and when it fails, we have learned to suspect the patient rather

than the method. The uterine enlargement did not diminish satisfactorily following the first application, chiefly because an artificial menopause did not occur.

The introduction of radium into the uterine cavity in the treatment of menorrhagia, with or without fibromyomas, always incurs some slight risk of pelvic inflammation. But when all these factors had been taken into consideration a conservative radium technic was used to supplement the first treatment. Packing the vaginal cavity with radium has been advocated in lieu of the intra-uterine application. We have found that to supplement the vaginal packing with surface radium packs usually proves effective. The last treatment was given with the hope that it might prevent a repetition of the severe hemorrhage. An artificial menopause has been produced in similar cases, and occasionally small amounts of uterine bleeding have occurred.

**Case 3**—A woman, aged sixty-five years, registered at the Clinic May 9, 1924, complaining of vaginal blood spotting. Her past history was irrelevant except for a curettage and right salpingectomy and oophorectomy at forty years, with concurrent menopause. She had never been pregnant. For two years before coming to the Clinic she had had leukorrhea which had become worse and was associated with some vaginal spotting of blood during the last year. She had noted slight abdominal discomfort at times, but never definite pain. Her weight loss had been insignificant. Slight dyspnea on exertion and occasional nocturia and dysuria were the only other complaints.

At examination the patient was rather obese, weighing 174 pounds. She was 5 feet tall. Her blood pressure was 210 systolic and 100 diastolic, her pulse rate 64, and temperature 98°. There was moderate dental and tonsillar sepsis. The eye-grounds showed a moderate retinal arteriosclerosis of the hypertension type. The heart was enlarged (4.5 by 16.5 cm.). Pelvic examination revealed a lacerated, slightly tender cervix, fixed in the pelvis. The fundus could not be outlined. The fixation was thought to be due either to an old inflammatory disease of the pelvis, which the history did not substantiate, or to the former operation. Special examinations were negative. Urinalysis revealed a moderate degree of pyuria, while the blood uric acid was 24 mg.

A diagnosis of obesity, essential hypertension and post-menopause uterine bleeding was made, and the patient hospitalized for five days' rest in bed. The blood pressure was lowered slightly and a diagnostic curettage was advised and performed. At operation, examination revealed a hard, adherent mass posteriorly in the culdesac, but difficulty of examination made the nature of the mass questionable. The pathologic report was atrophic.

endometrium. Four days later the patient was given intra-uterine treatment of 50 mg of radium for ten hours, and shortly afterward was dismissed, to report her condition in six months by letter.

*Comment*—These three cases demonstrate the possibility of hypertension as a possible factor in the production of uterine bleeding. The history and physical findings were of interest but not conclusive proof of this. The pelvic examination, dilatation, curettage with general anesthesia, pathologic report and the prophylactic intra-uterine application of radium, constitute the routine procedure in dealing with similar patients.

**Case 4**—An unmarried woman, aged fifty seven years, registered at the Clinic October 30, 1916. Her father died of inflammatory rheumatism, her mother of cancer of the breast, and one sister of "hypertension." The patient had had occasional attacks of tonsillitis and the menopause had occurred at fifty one and fifty-two years of age. A cyst of the cervix had been removed elsewhere in 1914. For five years, before coming to the Clinic, the patient had had a foul smelling vaginal discharge, necessitating her wearing a napkin constantly. She had also noted a painful area with a little tenderness in the left groin for "years." The onset of the pain was noted especially after overworking, and was never associated with menstruation.

Examination revealed an obese woman, not acutely ill, with moderate hypertrophic rhinitis, moderately infected tonsils, and several crowned teeth. Pelvic examination revealed that the cervix was normal both to inspection and palpation, but that there was moderate leukorrhea, the fundus was not palpable.

The blood pressure was 116 systolic and 85 diastolic, the pulse rate 82, and temperature 98°. Urinalysis revealed normal findings. The hemoglobin was 81 per cent. A dental x-ray disclosed a small abscess at the roots of the right first molar. A diagnosis of fatigue strain was made and the patient given a tonic and dismissed. She registered again at the Clinic July 11, 1921, at the age of sixty-five years. She had had influenza in 1921. At this time she had had a milky blood mixed vaginal discharge which had persisted for six months, with definite hemorrhages the last two months. The last marked uterine hemorrhage followed her visit to a sanatorium where she was undergoing hydrotherapy for "neuritis." At this time, a diagnostic curettage was performed which was reported negative by the pathologist. Six days after operation, intra-uterine radium, 100 mg for fourteen hours, was instituted to control the hemorrhages. Nine days later, another similar hemorrhage occurred, and the patient was told that she should have a hysterectomy.

Examination revealed obesity as on the previous visit, poor teeth, moderately infected tonsils and a systolic murmur over the entire precordium of the heart. Cardiac sounds were not well sustained. The abdomen was very obese, there was some atresia of the vagina, the cervix was hypertrophic

and the fundus was not palpable. There was a brownish discharge from the cervix, but no bleeding.

The patient's height was 5 feet, 6 inches, her weight 230 pounds. Her blood pressure was 180 systolic and 80 diastolic on two occasions. Her pulse rate was 76, and temperature 99°. Urinalysis revealed nothing abnormal. The hemoglobin was 74 per cent, the erythrocytes numbered 4,370,000, and the leukocytes 9,000. The Wassermann reaction on the blood was negative. The renal functional test (intravenous) was 25 per cent, blood urea 12 mg., and x-ray examination of the chest was negative. Electrocardiographic examination August 11, 1924, when the patient had been on digitalis for one week, showed inverted T-wave in Derivations I and II, with an arborization block, and QRS interval of 0.14 of a second. Another electrocardiographic examination, one week later, without digitalis, confirmed the findings of the first test.

A diagnosis of benign hypertension, with vascular and myocardial degeneration, was made, and it was thought that further radium treatment or surgery (hysterectomy) was contraindicated. Medical management with reduction of weight was advised, and the patient was sent to the Calorie Kitchen. On the reduction diet she lost 10 pounds in one week, and the blood pressure was reduced to 144 systolic and 80 diastolic. She was dismissed to continue similar treatment at home.

*Comment*—On consultation, it was fairly well established and firmly believed by the patient that on two occasions the uterine bleeding was definitely related to vigorous hydrotherapy. Considering that the hypertension was of the fluctuating type, it is possible that this relationship was compensatory, and thus prevented cerebral drainage. The vaginal discharge was never typical of carcinoma, the bimanual and visual examination of the parts and the long history substantiated this opinion. The patient feared cancer and urged that everything be done to rule it out at this time, and, if present, to institute the recognized methods of treatment. The recent dilatation and curettage and intra-uterine application of radium, and the pathologic report that no cancer elsewhere was found, were sufficient to contra-indicate surgical intervention as well as further irradiation at this time. The surgical risk involved in this case in proving the presence of a carcinoma of the fundus of the uterus was too great, in view of the scant evidence.

Case 5—A boy, aged fifteen years, registered at the Clinic May 14, 1924, complaining of headaches, nausea and vomiting for fourteen months. His

previous illnesses included tonsillitis, scarlatina, and influenza. In 1918 tonsillectomy had been performed and in September, 1922, he had been thrown from a steer, striking the right side of his head. His present illness began about six months after the injury to his head, when he noticed aching pain over the left eye which shortly spread over the entire head. At the same time, his gait became unsteady. Then he had spells of sudden vomiting, often of the projectile type, and usually without nausea beforehand. He also complained of dimness of vision in the left eye, and slight deafness in the left ear. The last five or six weeks before coming to the Clinic he had had fairly severe pain, most noticeable in the back of the head, and quite unrelated to his vomiting attacks, but brought on, he thinks, by straining, walking, and so forth. He had always been of a nervous temperament and easily excited, but his father considered his mentality normal. Constipation was his only other complaint.

At examination the patient seemed fairly well nourished, he had an ataxic gait, marked nystagmus, and pupillary reactions sluggish to light. Bilateral tonsillar tags remained with considerable scarring. Patellar reflexes were suggested. His blood pressure was 100 systolic, 65 diastolic, pulse rate 80, and temperature 98°. A twelve-hour specimen of urine had a specific gravity of 1.032, it was slightly alkaline, contained a trace of albumin, and a few pus cells, but no sugar. The hemoglobin was 95 per cent, the erythrocytes numbered 5,200,000, and the leukocytes 19,000, 10,000 and 8,000 respectively, on three occasions. The blood Wassermann reaction was negative, the blood urea, 32 mg. X-Ray examination of the chest was negative. X-Ray examination of the head showed "evidence of intracranial pressure." After a special neurologic examination the diagnosis of a left cerebellar tumor with a questionable angle tumor was made.

Exploration and decompression was performed May 23. A tumor was seen to involve the lower third of the left cerebellum which had prolapsed into the foramen magnum below the inferior margin of the atlas. Because of the extent of the lesion, only a portion of the tumor was resected. The pathologic report was "glioma, quite vascular and cellular."

June 10, palliative radium treatment was instituted and during the next five days the patient received 18,000 mg hours of radium, using blocks of Balsa wood 5 cm thick and 7.5 cm square at the base, filtration, 2.0 mm rubber, 200 mg of radium for nine areas over the posterior half of the head for ten hours to each area. The patient was then dismissed and advised to report in three months. He was seen again September 15, and while still complaining of difficulty in walking and early morning nausea, with frequent vomiting, he had had no headaches nor visual disturbance, had gained 15 pounds, and was doing light work on the farm. More palliative radium treatment was begun September 17 with the same technic as before, except that twelve areas were outlined. Consequently a total of 24,000 mg hours of radium was given in six days. During the treatment, the patient experienced some nausea and vomiting, and felt a little weak. He was dismissed September 23, having made a satisfactory response to the radium treatment.

*Comment*—The use of radiotherapy for brain tumors furnishes some astonishing results, but the work is too new to draw any conclusions. Brain tumors should be explored and every effort made to determine their character, location, and extent, and to remove them when possible. A careful microscopic study is of value since the very cellular type of gliomas responds well to radium packs to the head in the region of the tumor, and when centrally located a thorough crossfire technic should be employed. Radium packs can be supplemented with roentgen-ray treatment, or the latter may be used alone. I am confident that the neurologic surgeon has a valuable adjunct in radium and roentgen-ray treatment.

**Case 6**—A man, aged thirty-one years, registered at the Clinic December 12, 1921, complaining of lower abdominal pain. His father had died of tuberculosis at sixty-eight years of age. He, himself, had had malaria three times in childhood, influenza in 1920, gonorrhea in 1915, and syphilis in 1918, with salvarsan treatment subsequently. In 1920 hemorrhoidectomy had been performed and the left testicle excised. He had been married six years, and had one child two and one-half years old who was well. He used tobacco excessively, and had recently used morphin. His present illness began with the sudden appearance of a swelling of the left testicle in February, 1920, which within one week became about 8 cm in diameter, but was painless and hard. The testicle remained hard, and slowly but progressively increased in size for two months. The patient was then taken with influenza which lasted ten days, during which time the testicular tumor returned to nearly normal size, only to enlarge again to its former size as soon as he was up and about. In April, 1920, the left testicle was removed elsewhere, and a pathologic diagnosis of "small round-cell sarcoma" was made. Thereafter he felt perfectly well until three months before coming to the Clinic, when he was awakened early one morning with dull pain in the lower back and lower abdomen, especially in the right lower quadrant. This seemed to be relieved by the passage of flatus, but the pain continued intermittently.

At examination the patient was undeveloped and undernourished, weighing 123 pounds, which he stated was 8 pounds less than his average weight. His blood pressure was 120 systolic, and 75 diastolic, pulse rate 78, and temperature 98.8°. Pupillary reactions were sluggish to both light and accommodation. The pharynx and tonsils were considerably injected. The cervical and inguinal lymph nodes were bilaterally palpable.

In the abdomen was found a hard, firm, irregular mass (Fig. 224, a) in the epigastrum and left hypochondrium, and another mass (Fig. 224, b) 3 cm in diameter, firmly fixed 5 cm to the right of the umbilicus. The stomach was outlined below (Fig. 224, c) by succussion. Both patellar and

Achilles' reflexes were exaggerated. Urinalysis was negative, the hemoglobin was 75 per cent, the leukocytes numbered 7,900, and the blood Wassermann reaction was negative on two occasions. Gastric analysis revealed

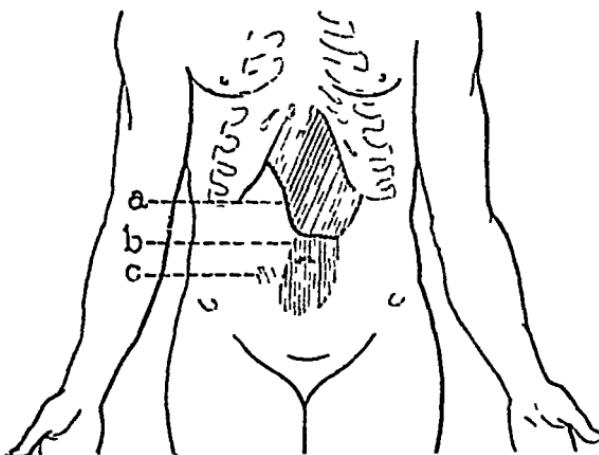


Fig. 224.—Outline of masses in the abdomen

total acidity 32, free hydrochloric acid 14, quantity 50 c.c. X-ray examination of the stomach, kidneys, ureters, bladder, and lungs was negative. A special neurologic examination was negative.

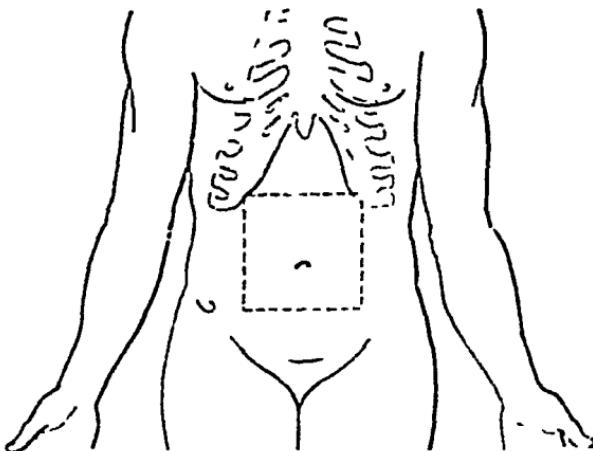


Fig. 225.—Area of thickness in the abdomen as a result of treatment

The case was considered primarily one of retroperitoneal metastases from sarcoma of the left testicle, and radium treatment was recommended. The patient received a total of 21,500 mg. hours of radium in topical applica-

tions over the abdominal masses, during a period of four days. The pain in the abdomen and back stopped after the first six hours' treatment. There was no severe reaction, but the patient complained of slight nausea. Roentgen-ray treatment of moderately high voltage (135 kilovolts) was then instituted over the back and part of the abdomen which had not been treated by radium. The patient was then dismissed to return in two months. On his return he complained of a recurrence of the old abdominal pain ("gas pains") and pain in the lumbar region, for the last five days. He weighed 138 pounds, and had been working regularly for some time.

Examination March 4, 1922, revealed no palpable abdominal masses. There was one small lymph node, 1 cm. in diameter, in the left anterior supraclavicular area, over which topical applications of radium were applied (3,300 mg hours). Further roentgen-ray treatment, covering the area of the entire abdomen, chest and back, with a moderately high voltage (135 kilovolts), technic as before, was also carried out. In July, 1924, the patient returned for a check-up examination, which was negative for any evidence of activity, but there was a definite area of fibrosis and telangiectasia in the anterior abdominal wall (Fig 225).

*Comment*—Patients with metastatic testicular tumors are of great interest to the radiotherapist. Clinically, they represent a group in which most of the major abdominal operations are performed without relief to the patient. The primary tumor, when removed, does not recur to such an extent that the examining physician is impressed with its significance. Metastatic tumors seem to occur very early, and soon give symptoms simulating certain of the major abdominal complaints. They may defy palpation and are bizarre in form and location. I have seen patients with metastatic tumors who have had appendectomy, cholecystectomy, gastro-enterostomy, or exploration, for removal of a possible primary tumor of the kidney, and dissection of the superficial glandular enlargements usually in the left supraclavicular space. The glands in the neck soon recurred. I recall one patient who came to the Clinic with the history of an exploratory abdominal operation which revealed an inoperable abdominal tumor, the primary testicular tumor had been overlooked.

The radiotherapist encounters many hopeless patients, a few of whom are among this group with metastatic testicular tumors. The primary response to surface radium packs is astonishing and the result may endure for from two to three

years, one patient in my series has been well for five years. The radium packs to the abdominal wall overlying the palpable tumor should be supplemented with roentgen-ray treatment of the back and opposite lateral wall. As soon as surgical convalescence following removal of the primary tumor will permit, the early cases should be followed with deep roentgen-ray therapy, the beam of therapeutic rays being directed to the lumbar and renal lymphatics. This should be the routine in all cases rather than to wait until signs of the new growth develop.

**Case 7**—A man, aged eighteen years, registered at the Clinic June 9, 1924, on account of very obstinate constipation of six weeks' duration. He had had pneumonia and tonsillitis when a child, and influenza in 1918. His present complaint began six weeks before examination, with cramp-like pains across the lower abdomen, lasting one day. This was soon followed by an increasingly obstinate constipation, although previously the bowels had always been regular, and the stools well formed. Cathartics were taken in progressive doses, until it seemed that no remedy was of value. On consulting a physician he was told that he had a malignant tumor of the rectum and prostate. Twice there was a slight amount of blood in the bowel movements. His weight loss was 12 pounds during this period. No other abdominal discomfort or pain was experienced.

At examination the patient was well developed and well nourished, but weighed only 124 pounds, whereas his normal weight was 160 pounds. He was 5 feet, 6 inches tall. His blood pressure was 120 systolic and 80 diastolic. A large, hard, irregularly nodular mass which practically closed the lumen of the bowel was palpated in the rectum. There was also some abdominal distention. Proctoscopic examination revealed a low rectal lesion constricting the lumen of the bowel to a diameter of about 1 cm., just above the anus, and fixed in a large pelvic mass, evidently malignant. Urinalysis gave normal findings; the hemoglobin was 79 per cent, the erythrocytes numbered 4,400,000, and the leukocytes 8,000. The blood Wassermann reaction was negative. X-Ray examination of the chest was negative.

At surgical consultation, it was decided to perform a colostomy and exploratory operation. A left rectus modified Miltzer type of colostomy was performed, and an extensive growth in the middle and upper rectum was found to be firmly adherent to the bladder and prostate. A few small, but apparently circumscribed, nodules were found in the cecum, posteriorly. The liver was not affected. The condition was considered questionably operable, and further operative procedure was not to be considered until after radium and x-ray treatment. Two weeks after operation the patient received 12,600 m.<sub>h</sub> hours of radium, including 50 m.<sub>h</sub> for fourteen hours, by rectal applicator on four occasions, the rest being given in topical applications over the inguinal glands on both sides, which were considered definitely malignant. High voltage x-ray treatment over the pelvis both anteriorly

and posteriorly, was then instituted. The patient was seen again two months later, September 17. The condition was not yet considered surgical, and he was referred for further radium and x-ray treatment. He received 10,800 mg hours of radium, including 50 mg for fourteen hours with a rectal applicator, repeated on two occasions, the rest being given in topical applications over both inguinal regions. He was then given high voltage (200 kilovolts) roentgen-ray treatment over the pelvis at 50 cm distance, with filtration of copper 2.0 mm, aluminum 2.0 mm for three hours and extending over a period of six days. His general condition was good, and he said he had felt like working the last month. He gained 25 pounds weight, and his strength had been increasing steadily. The colostomy was functioning perfectly and regularly, though there was some discharge of mucus from the rectum, but no more bleeding.

*Comment*—Cancer of the rectum in a young adult is comparatively rare. The growths are usually inoperable when first seen at the Clinic. Owing to the youth of the patients and their resistance to disease, everything possible is done to rid them of the new growth. The few that I have had to treat following a permanent colostomy and posterior resection have usually recurred and their response to treatment was only mediocre. Exploration and permanent colostomy is indicated. If a posterior resection is too great a risk and if the tumor is an adenocarcinoma, irradiation can be relied on to produce definite palliation.

The initial response in this case is satisfactory so far, and the patient will probably receive much relief from the radiotherapy alone.

**Case 8**—A woman, aged fifty-two years, registered at the Clinic June 23, 1924, complaining of a lump in the vagina. An uncle and aunt had died of cancer of the face. The patient had had tonsillitis frequently, rheumatic fever in 1902, pneumonia in childhood, meningitis (?) when twenty-two years of age, and a miscarriage at two months. She had been married seventeen years, and had one child who is living and well. Her menstrual history had been normal, the menopause occurring at fifty. For a year or two before coming to the Clinic she was lacking in energy. Five months before, she noted a lump in the vagina. One month later, she began having slight bloody vaginal discharges, the first lasting one day. After the lump was noted, the patient had repeatedly seen "polypi" in the water following a douche. Pain of a rather sharp, lancinating character had been felt at times over the lower abdomen and radiating into the vagina. Pain had also been noted in the hips and lower spine, which for the last two months had been aggravated on

reclining. The patient had nocturia occasionally, and for six or seven years had had intermittent attacks of dysuria, associated, she said, with leukorrhea. Recently, the urinary stream had been considerably smaller than normal, owing, she thought, to the growing vaginal mass.

Examination revealed that the patient was fairly well generally, 5 feet, 4 1/2 inches in height, and weighed 152 pounds. The blood pressure was 142 systolic and 82 diastolic, the pulse rate was 80 and the temperature 99°. The teeth showed much dentistry and their condition was questionable. Examination otherwise was negative except that of the pelvis. There was a massive, necrotic tumor in the vagina, infiltrating the vaginal walls, broad ligaments, and extending around the ureters. The whole mass was firmly fixed. There was a possibility that part of it was a distended bladder, and, therefore, a gradual decompression was instituted. A foul discharge was present. The left inguinal glands were small but tender.

A diagnosis of carcinoma of the cervix with extension to the vaginal wall and broad ligaments was made. Because of the difficulty of placing radium applicators into the mass, it was considered advisable to institute deep x-ray treatment. Eight treatments of 200 kilovolts at 50 cm. distance for three hours daily (two periods of one and one half hours each) using filtration of 2 mm. copper and 2 mm. aluminum were given. The areas treated included the entire pelvis, anterior, posterior and lateral aspects, and the treatment lasted ten days. This treatment relieved the pain in the back and increased urinary control. She was then given 2,100 mg. hours of radium in one week, in frictional dosages of 50 mg. each for fourteen hours, in a vaginal applicator, 1 mm. brass filtration. Palliation was all that could be hoped for, but when the patient was dismissed July 15, about three weeks after the first x-ray treatment had been instituted, marked improvement was evident. She was urinating freely, without urgency or frequency, although with some dysuria, whereas several times before and during part of the radiotherapy she had been unable to void without catheterization. Ten days later when seen again she was continuing to improve, and had no urinary symptoms except slight burning on micturition.

*Comment*—This patient is typical of those with massive carcinoma of the cervix with wide fixation and general health markedly undermined. Among radiotherapists, it is today a much mooted question, whether or not irradiation should be attempted. The general condition of the patients will not permit a prolonged examination to determine the possibility of complications, and, as a rule, regardless of the findings even after a searching investigation, treatment is usually given. The usual complications are bilateral or unilateral hydronephrosis, and rectovaginal or vesicovaginal fistula, especially if there is much crater formation or ulceration, or low grade obstruction.

due to involvement of the broad ligaments, or sacral lymphatics. For relief of the obstruction a colostomy may be necessary. The pain is usually intense and unrelenting. I have observed similar cases in which I felt reasonably sure that these complications were prevented. In similar cases my criterion for treatment has been to determine whether the patient's general health is such that she has a chance of living at least six weeks, since this interval is usually necessary for most of the benefits from irradiation to occur. Cautious treatment is recommended. In this instance, the response was striking and almost immediate. There was little, if any, systemic reaction. The bladder complaint gradually cleared up, the pain became less, and there was a gradual improvement of the general condition. Today the patient is seemingly free from symptoms and I am confident that our endeavors have been greatly appreciated. I am sure that this group of cases is worthy of a cautious trial treatment. The palliation that is possible in some cases is astonishing.

**Case 9**—A woman, aged thirty-four years, registered at the Clinic June 14, 1920, complaining of abdominal cramp-like pain. One sister had died from tuberculosis. The patient had had diphtheria, pneumonia and malaria when a child, and tonsillitis and "grippe." She had been married nine years and had two children living and well. She had had one miscarriage, eighteen months before examination here. The menses had been irregular, occurring every three and one-half to four and one-half weeks, quite painful and profuse at times, but usually moderate. She had had leukorrhea for many years. In 1914 she had had appendectomy and a right oophorectomy elsewhere. For the last eighteen months she had had crampy pains over the lower abdomen, almost daily, but never very severe. She said that she had had leukorrhea for years, but that it had become worse the last eight months with a foul odor, especially during menstruation. Three months before examination, the family physician found a growth, about 2.5 by 3.5 cm., in the urethra which was diagnosed "urethral caruncle", this had been removed elsewhere six weeks before, the pathologic report being negative for malignancy. Since then she had complained of constant, dull pain across the lumbar region. Her appetite was only fair, constipation was marked. She had occasional nocturia and passed only small amounts of urine with intermittent spells of dysuria and hematuria.

Examination showed that the patient was underdeveloped and poorly nourished and weighed 118 pounds. Her blood pressure was 120 systolic and 75 diastolic, pulse rate 80, and temperature 99°. The teeth evidenced considerable pyorrhea, and periapical infection. Moderate tenderness was elicited over both lower quadrants of the abdomen. There was a slightly

reddened area about the urethral meatus and a remnant of what was thought to be a urethral caruncle. The cervix was firm and nodular on the left, and without ulceration. A specimen for biopsy from the remnant of caruncle was reported to be epithelioma, and after surgical consultation radium was advised, using 200 mg hours over the lesion with moderate voltage x-ray over the inguinal glands, bilaterally, over the lower abdomen and lower lumbar region.

The patient was seen again August 20. She complained of slight dysuria, and nocturia. She felt well, had gained in weight and strength, and no longer had the lower abdominal pain. There had been no reaction following the radium and x-ray treatment. The urethral orifice appeared to be normal and without induration. The inguinal glands were palpable on either side. Moderate voltage x-ray treatment was applied bilaterally over the inguinal glands.

November 20, the patient returned to the Clinic without any urinary symptoms, but with menopause evident from four months' cessation of the menses and intermittent "hot flashes." Otherwise, she felt well and said that she had been working hard. Examination was negative except for suspicious right inguinal glands which were given a similar x-ray treatment as on previous occasions. March 3, 1921, the urethral condition was normal. She had lost 5 pounds and had many vague sensations, apparently psychotic with a dementia praecox trend. August 22, she complained of dysuria and occasional suprapubic pains, but was well otherwise. Examination revealed no activity about the urethra. x-Ray examination of the chest was negative. The menopause symptoms were considered as due to the x-ray and radium treatment. As the inguinal glands were still suspicious, 5,000 mg hours of radium in topical applications were applied, divided over either groin, as a prophylactic treatment.

While the patient did not return to the Clinic again, she reported by correspondence and through her family physician that her general condition was excellent, that there was no recurrence of the urethral lesion, and that in June, 1924, her weight was 148 pounds, a gain of 20 pounds since treatment was first instituted. Her last report, October 20, 1924, states that her general condition is poor, but does not mention a recurrence, five years since her first treatment.

*Comment*—Carcinoma of the urethra can be favorably influenced with radium and roentgen rays, and in some cases the palliation is astonishing, especially in those cases in which the primary lesion is small and without inguinal glandular involvement. In this case the primary lesion had been modified by a previous operation which made the extent of the new growth doubtful. The inguinal glands were definitely enlarged and clinically malignant. In the management of lesions of this type and location every effort should be made to apply sufficient

treatment to the primary growth, and to avoid, in every possible way, further damage to the external urethra, which might cause secondary contracture and closure of the part. In all cases the inguinal glands should be treated as if malignant.

Case 10.—An obese woman, aged forty-five years, came to the Clinic July 16, 1923, with a history of intermittent vaginal bleeding for six months. Her mother had died from "Bright's disease." The patient had had diphtheria and tonsillitis when a child, and pneumonia and pleurisy seven years before coming to the Clinic. Menstruation had been normal. She was married, had had four children who were living and well, and two miscarriages. Hysterectomy for "tumor" and appendectomy had been performed elsewhere in June, 1921. The present illness began four years before examination, with vomiting spells soon after breakfast, amenorrhea and considerable constipation. The patient had never had abdominal pain or jaundice, although the vomitus consisted usually of a greenish mucus-like fluid. She was thought to have had gall-bladder trouble, but the gall-bladder was normal when the biliary tract was explored at the time of the operation in June, 1921. Following the operation, she gained 40 pounds and felt fairly well until the last six months, when she noted a slight bright red vaginal discharge which had persisted intermittently to date. Occasionally the blood was mixed with a foul yellowish discharge. She complained of slight pain occurring in the right lower quadrant of the abdomen at times, with pain radiating down the right thigh to the knee. Her appetite was good, but the constipation was marked. She tired readily and experienced moderate dyspnea on exertion.

The physical examination and laboratory reports were practically negative. The patient's obesity made the pelvic examination tedious. There were multiple hard infiltrating masses deep in the vagina, the largest about 4 to 5 cm in diameter. There was a purulent sanguineous discharge with odor. A rectal examination revealed a hard fixed mass in the left broad ligament, size 3, and one in the right broad ligament, size 2.

Palliation was all that seemed possible from any type of treatment, and, therefore, radium and roentgen-ray treatment was recommended. Eight radium applications were made to the involved area in the vagina, and a course of deep roentgen-ray treatment was directed to the lower abdomen and back. The initial response was very gratifying in spite of the fact that the tumor was very hard to treat, since the patient cooperated poorly. She complained constantly about a painful and tender vagina. She returned during the latter part of September with the statement from her family physician that there was a small node in the vagina, and we felt confident that further treatment was indicated. The morale of the patient was greatly improved. There was a slight increase in weight and a return of her old trouble of slight bleeding and spotting following trauma to the part. Otherwise there was no discharge. The menopause symptoms were severe for a time, then gradually subsided. All pains disappeared. A vaginal examination revealed that the infiltrating masses had disappeared, but further anteriorly there was a nodular mass about 2 cm in diameter. Clinically, it was a

new expression of her old trouble. The broad ligament infiltration was greatly reduced, probably 95 per cent, which accounted for the absence of pain. Since the primary lesion had responded so satisfactorily, we felt reasonably sure that the new growth would be favorably influenced by further irradiation.

*Comment*—This case demonstrates the effectiveness of the initial intensive application of radium in broken doses in advanced carcinoma of the cervix. In this instance, there had been a partial operation elsewhere for the removal of the malignancy. The initial response to the first treatment was very gratifying. The deeper portions of the vaginal cavity were rendered smooth and free from apparent disease. The infiltration in the broad ligaments was greatly reduced, which accounts for the absence of the pain. It is questionable today whether or not radium treatments should be continued if the first treatment fails. We are confident that our intensive initial treatment should never be repeated.

This patient belongs in the group in which there are definite lesions in the vaginal wall beyond the field of the former treatments. With appropriate treatment such lesions can certainly be reduced, thus avoiding otherwise inevitable complications, such as a rectovaginal, or a vesicovaginal fistula, and obstruction of the external urethra, and so forth. If three or four vaginal treatments are applied to the tumor, and Roentgen ray is delivered to the lower abdomen and back, the local expressions of the disease can be retarded.

## RADIOTHERAPY IN FOUR UNUSUAL CASES OF MALIGNANT TUMOR

ARTHUR U DESJARDINS

The four cases reported here are intended to bring out certain interesting features of radiotherapy as applied to different types of malignant tumors

Case 1.—A man, aged fifty-six years, came to the Clinic June 11, 1923 because of "neuritis in the shoulder and back." A growth had been removed from his right thigh at the age of sixteen years. His tonsils had been removed in 1920 because of a mild arthritis, which disappeared shortly afterward. In December, 1922, pain gradually appeared in the back, then remained stationary. The pain was made worse by moving the shoulder, and also by bad weather. Later the backache had been replaced by a pain in the left hip which was associated with an intense pleuritis and nocturia (two or three times). With the onset of the foregoing symptoms, pain appeared in the right side, and radiated downward toward the scrotum. In January, 1923, severe pain with hematuria occurred, lasting all day, and finally a stone, about 0.75 cm in diameter, was passed. A gradually increasing swelling of the left buttock had been noted during the previous five months.

The patient's height was 72 inches, his weight 160 pounds (normal weight 185 pounds), the loss of 25 pounds having occurred during the previous six months. He was moderately pale, and had an old median-dorsal kyphosis (symptomless). On the right buttock was a large, somewhat diffuse mass over, and firmly attached to, the posterior portion of the left ilium. The mass was fairly smooth, hard, slightly tender, and interfered with walking. Over the right scapula was another large, fairly smooth, hard tumefaction firmly fixed to the scapula. The movements of the right upper extremity were seriously hampered by the mechanical interference and the resulting pain. There were old scars on the legs and back. The prostate gland was normal. The systolic blood pressure was 170, the diastolic 90. The temperature and pulse rate were normal. The hemoglobin was 75 per cent, the erythrocytes numbered 4,800,000, the leukocytes 8,000. Examination of the urine was negative. Roentgenologic examination revealed the presence of hypertrophic arthritis of the right shoulder and scapula, and sarcoma of the scapula with disorganization of the avicular border of the bone. In the pelvis was what appeared to be an osteochondroma involving the left ilium and ischium. The supraacetabular portion of the bone was chiefly concerned.

Since both these tumors were inoperable because of their size, location and fixation to the bony structures from which they sprang, the patient was referred to the Section on Radiotherapy without preliminary biopsy, which was not considered justifiable.

June 18 and 19, 1923, a first course of high voltage x-ray treatment was given, both tumors being attacked from three directions (anterior, lateral and posterior). The patient returned August 8, feeling distinctly better, he was able to walk more freely, and the pain had subsided considerably. Between August 9 and 11, he was given a second course of high voltage x-ray treatment, practically duplicating the first course. November 12, his condition was markedly improved in every way. The large scapular tumor had completely disappeared, and the right upper extremity could be moved freely. The tumor of the left ilium and buttock had also decreased greatly, but there was still a little pain in this region when the patient walked. Roentgenologic examination of the right scapula confirmed the clinical appearance of improvement, and showed that the bony destruction not only was arrested but beginning to repair, the left iliac tumor was also definitely improved, but not so markedly. Between November 15 and 21, a third course of high voltage x-ray treatment, the same as the second course, was given. February 18, 1924, the patient weighed 180 pounds. The tumors of the scapula and ilium were no longer palpable, but the patient was distinctly pale. However, the blood count showed no essential change except in the leukocytes, which were reduced to 4,800, undoubtedly by the x-ray treatment. Roentgenologically the destructive process in the right scapula and left ilium had apparently stopped, and there was distinct evidence of regeneration. A fourth course of high voltage x-ray treatment, directed only to the iliac tumor, was given February 19, 20, and 21. No other treatment was given. The patient's family physician has written several times since to say that the patient has improved steadily, he has been working for more than twelve months.

*Comment*—There are several interesting points in this case. First, there were two separate tumors, both voluminous and so nearly equal in size as to make it impossible to decide whether one was secondary or whether they were entirely distinct neoplasms. Clinically and roentgenographically they resembled each other closely. From the examinations it appeared that they belonged to the sarcoma group, but in the absence of a biopsy this could not be ascertained. However, judged by their reaction to x-rays they were probably chondrosarcomas. In any event, both tumors have clinically disappeared as the result of four courses of x-ray treatment at high voltage (200 peak K. V., I. S. D. = 50 cm., filtration = Cu 0.75 mm and Al 10 mm., each of three fields receiving 5 milliamperes for one hour and

thirty minutes) In view of the well-known pernicious tendencies of sarcoma it would be too much to expect permanent cure in such a case, nevertheless, considering the fact that no other form of treatment offered any hope of bringing about even temporary improvement, and that the patient's life was a question of a few miserable months, the primary result is decidedly worth while

**Case 2** —A man, aged thirty-nine years, registered at the Clinic October 30, 1922 September 15, 1921 his left testicle, which had grown larger steadily for a year and a half, was removed, and a diagnosis of sarcoma made. He was fairly well until April, 1922, when, for two or three weeks, he had a "sick spell" with pain in the upper abdomen, accompanied by the loss of 15 to 20 pounds in weight. He recovered, and regained some of the lost weight. A month before coming to the Clinic he had begun to have pain in the left epigastrum and left hypochondrium, radiating around the left side to the back. This pain was continuous during the subsequent month and was worse at night. He was given medicine by his physician, but without relief. At the time he registered at the Clinic he thought the pain was subsiding, perhaps because he had spent the last three weeks in bed. His appetite was fairly good. His home physician had discovered a mass in the upper left quadrant of the abdomen about two weeks previously, this seemed to be increasing in size.

The patient was large-framed, well-developed, and well nourished, although he was a little pale. On the skin of the back was a large, mottled, pigmented area, the result of mustard plasters. The teeth were in bad condition with marked pyorrhea. A few slightly enlarged lymph nodes were palpable in the inguinal regions. The mass in the left upper quadrant was quite large, somewhat irregular, very firm, and extended beneath the inner portion of the left costal region well over to within 1 cm of the right mid-clavicular line and 4 cm. below the umbilicus, it did not move with respiration. The hemoglobin was 75 per cent, the erythrocytes numbered 4,500,000, the leukocytes 5,500. The Wassermann reaction was negative. Roentgenologic examination of the thorax disclosed elevation of the diaphragm on both sides, the lungs appeared normal. A clinical diagnosis of metastasis to the retroperitoneal lymph nodes from a tumor primary in the left testicle was made and the patient was referred for radiation treatment.

Between November 1 and 9, 1922, an extensive radium pack, consisting of a total of 21,842 milligram hours, was applied over the region of the tumor anteriorly and over a portion of the left side. This was supplemented between November 10 and 15 by an extensive course of x-ray treatment at moderate voltage directed to the region of the tumor through the back and also to the mediastinum, in spite of the fact that evidence of metastasis in the latter region could not be demonstrated. The patient was then allowed to return home and arrangements were made with a competent local radiologist to give him a second course of x-ray treatment at high voltage, this was

done December 18, 19, 20, and 21. A third course, also at high voltage, was given January 20 and 30, 1923. The patient tolerated the radiation quite well. Between November, 1922, and February, 1923, he had gained a few pounds in weight and appeared very much better. The tumor in the left upper abdomen was so much smaller that on abdominal palpation only a deep, flattish, indurated mass could be felt to the left of the spine, and extending from the umbilical region toward the left costal margin. One or two slightly enlarged lymph nodes were palpable in each groin. Between February 26 and March 3 another extensive course of x-ray treatment at moderate voltage was directed to practically the entire trunk.

The patient returned to the Clinic July 31, 1923, his general condition was greatly improved, the only complaint being a vague occasional drawing sensation about the abdomen, but without localization. Abdominal palpation was absolutely negative. He was allowed to return home without treatment, but his physician was requested to keep him under fairly close observation.

May 27, 1924, when he returned to the Clinic he was the picture of vigor and health, having gained 70 pounds and having worked steadily since early in 1923. He came for examination, because he did not care to take any chances. When seen again September 12, 1924, he still felt well, and had gained 6 pounds more. One night about two weeks previously he had had a sharp attack of pain through the middle and lower part of the back extending through to the upper abdomen and radiating to both shoulders. This had lasted for a few hours, but subsided after his physician had given him a hypodermic injection. He went to work the following morning as usual and had had no similar disturbance. Examination failed to reveal any evidence of recurrence.

*Comment*—The tumor in this case is typical of those which spring from the spermatogonial cells, and are generally classified as seminomas. Such tumors nearly always react quickly and in pronounced manner to even a moderate dose of radium or  $\gamma$ -rays, so that a voluminous tumor will melt away in a relatively short time. This is in complete harmony with the well-known striking radiosensitivity of the normal spermatogonia with which these tumors are related. I cite the case, not so much to show the beneficial effect of radiation treatment, but to bring out the fact that the rate and degree of reaction to such treatment is so characteristic of this type of tumor that it can be used to distinguish it from any of the other types that are much more resistant to radiation. A typical carcinoma or a true teratoma of the testicle may respond to some extent to a ray or radium treatment but never with anything like the promptness or to

the same degree, as a seminoma. This fact could be made use of as a sort of therapeutic test whenever it is not feasible to obtain a biopsy, because it constitutes at the same time the best form of treatment for such tumors, in the majority of which surgical excision is out of the question. The only other types of tumor that might offer difficulty in differential diagnosis from the standpoint of susceptibility to radiation, are those belonging to the lymphoblastoma group, but the clinical features of the latter are sufficiently definite in most cases to enable one to distinguish them readily.

Case 3.—A woman, aged sixty-two years, came to the Clinic February 4, 1922, because of a swelling on the head, a choking sensation, and ringing in the ears. One aunt had died of cancer. In 1894 the patient had undergone a curettage, amputation of the cervix and perineorrhaphy, in 1904, appendectomy and cholecystectomy, and in 1919 an operation for goiter. One year previously, while combing her hair, she had noticed a swelling about 20 cm in diameter, a little to the left of the bregma. It was soft and painless. Since that time it had increased somewhat in size. There was no history of trauma except that when a child she had bumped her head against a log. Since November, 1921, she had had a choking sensation not accompanied by cough or hoarseness. She thought her neck was larger and she complained of dyspnea on exertion. The ringing in the ears had begun in December, 1921, she noticed it only when her attention was not elsewhere. There was no vertigo or deafness. Her weight was essentially normal at 145.

On examination a large soft fluctuating mass was found over the bregma, where an irregular area of the skull was absent. The larynx was pushed to the right, and the left lobe of the thyroid was firm and nodular, but there was no adhesion to the skin. The supraclavicular lymphatic nodes on the right side were hard. There was evidence of sclerosis, and there was slight varicosity of the veins of the leg. The systolic blood pressure was 168, the diastolic 88. The erythrocytes numbered 4,350,000, the leukocytes 4,506, the hemoglobin was 75 per cent. The urine was normal. The Wassermann reaction was negative. Roentgenologic examination of the skull disclosed a large area of destruction in both parietal bones adjoining the sagittal suture. A clinical diagnosis was made of carcinoma of the thyroid with metastasis to the skull.

February 17, 1922, a gland was excised from the left supraclavicular region and a specimen removed from the thyroid, microscopic examination of both proved the condition to be carcinoma. At the same time 50 mg of radium distributed in five steel needles were inserted in the thyroid gland and left in place for twenty-four hours (1,200 mg hours). As soon as the patient was able to leave the hospital (between February 28 and March 1) she was given a course of x-ray treatment directed to the thyroid through the

right side of the neck as well as to the mediastinum. The dosage used was voltige 135 peak K V, F S D 12 in., filtration copper 0.5 mm and aluminum 1.0 mm, 5 milliamperes, and time thirty minutes to each field.

Examination, April 4, showed that the tumor of the thyroid had flattened considerably, but the patient had lost about 10 pounds in weight. However, she had had flu one month previously. April 5, the tumor was again treated with radium, a total dose of 2,800 mg hours being delivered from the surface. This was again supplemented by x-ray treatment April 3 and 4, under the same conditions, the metastatic areas in the skull receiving a similar dose.

June 6, the patient's general condition was good and the thyroid enlargement had subsided still further. A roentgenologic examination of the skull showed no change, the areas of destruction measuring approximately 6 by 6 cm. A third course of radium (2,800 mg hours) was topically applied to the left lobe of the thyroid and left suprACLAVICULAR regions, and between June 7 and 10 the skull, together with the right lobe of the thyroid and right side of the neck, were treated by means of x-rays.

July 19, the tumor of the thyroid was represented merely by a zone of induration very much smaller in size. The areas of metastatic cranial destruction had apparently undergone no change. On this occasion radium treatment was not given, the x-ray treatment applied to the thyroid and skull was limited to the same conditions as previously.

August 30, the tumor of the head had increased in size with bulging, and the area of destruction measured 7.5 by 9 cm. The tumor of the thyroid could hardly be palpated. Between August 30 and September 2 another course of x-ray treatment was given.

October 16, it was found that the metastatic area on the skull had not increased since the patient's previous visit, and there was no sign of activity in the thyroid gland. x-Ray treatment was again given to both the skull and the neck, October 16 and 17, the dosage remaining the same.

December 18, the left lobe of the thyroid was very small, nodular and quite firm. The metastatic area in the skull had remained stationary. x-Rays were again applied to the neck and the skull December 18, 19, and 20.

February 16, 1923, the defect in the skull and the condition of the thyroid were about the same. x-Ray treatment was limited to the neck, and the dosage was the same.

May 15, the defect in the skull had diminished to 7 by 7 cm, the thyroid was still stationary. No treatment was given.

September 15, the patient was definitely more nervous and did not coordinate well. There was slight hesitation in her speech, slight sulcus in the left orbit, making the palpebral slit slightly narrower, there was no change in visual acuity, and no nystagmus. The defect in the skull had increased to 14 by 15 cm, extending on both sides of the median line, and there was definite bulging of the brain, probably accounting for the symptom. September 5, 6 and 7, x-ray treatment was directed solely to the skull with the same dosage, but concentrated toward the region of involvement through six fields.

October 8, considerable gain in strength was noted. The defect in the skull was 9 by 12 cm. All symptoms noted at the previous visit were much

improved. The metastatic area in the skull was again irradiated October 8, 9 and 10, along the same lines as in September.

December 6, the patient had been fairly well until about a week previously, when she began to feel faint and weak. Loss of appetite and slight loss in weight ensued. No evidence of activity in the thyroid was found. The metastatic defect in the skull had remained stationary.  $\text{x}$ -Ray treatment was given to the skull at the same voltage, but the distance was reduced to 30 cm, the filtration to 4 mm of aluminum, and 5 milliamperes for eight minutes were directed to each of four segments of the involved region. This was done with the idea of getting the bone to absorb as many  $\text{x}$ -rays as possible.

January 22, 1924, the patient was much better in every way, having gained in weight and strength (141 pounds), all previous symptoms had subsided. The defect in the skull measured 7 by 10 cm, there was no activity in the thyroid region. The  $\text{x}$ -ray treatment was repeated.

March 6, there were slight drawing sensations around the area of destruction on the skull, which now measured 7.5 by 9 cm.  $\text{x}$ -Rays were applied March 6 and 7, the technic being the same as in December and January, except that the distance was increased to 40 cm, and the time to thirty minutes.

April 7, the patient's general condition was relatively good. The area of destruction on the skull measured 9 by 11 cm. April 9 and 10 a course of high voltage  $\text{x}$ -ray treatment was given, the dosage being Voltage 200 peak K. V (sphere gap), distance 50 cm, filtration, copper 0.75 mm, and aluminum 2.0 mm, 5 milliamperes, and time one hour and twenty minutes to each of two fields.

June 3, the patient mentioned that her hands were slightly clumsy at times, but otherwise she had been well. The area on the skull was 8 by 11 cm. No treatment was given.

September 5, the patient's general condition was good. There was no extension of the defect in the skull. In fact, one had the impression of a partial bony regeneration in the form of a thin plate corresponding to the inner table.

*Comment*—Radiologists have known for some time that carcinoma of the thyroid shows a very distinct susceptibility to radiotherapy, this fact is corroborated by the behavior of the tumor in this case. At first there was some doubt as to the malignant nature of the destructive process in the skull, but the treatment completely dispelled such doubt, because the susceptibility of the metastasis corresponded so closely to the primary tumor in the thyroid gland, in spite of the fact that complete bony regeneration has not yet been achieved. As a matter of fact, this may never take place, and it may be impossible to keep the malignant process in the skull permanently.

in check. Had this been secondary to a carcinoma elsewhere than the thyroid, it is quite probable that its development would not have been checked to anything like the extent in this case, and death would long since have claimed another victim.

**Case 4** — A man, aged forty-nine years, registered at the Clinic August 7, 1924. One brother had died at the age of forty-two years, of sarcoma of the soft tissues of the thigh. Four and one half years before, while shaving, the patient had noticed under the left jaw a small, hard lump which was quite painless. This lump gradually increased in size, although varying somewhat from time to time, until two years before, when it was excised by the family physician. A tentative diagnosis of Hodgkin's disease was made. Shortly afterward another tumor developed rapidly, immediately in front of the scar. For the last two years the patient had had a great deal of "stomach trouble" in the form of distress after meals or after drinking, but which he did not think had any relation to the kind or quantity of food, he believed it to be due to gas distension, it was generally as bad at night as during the day. He had lost about 4 pounds during the previous six months. A few other lumps had developed over the upper thorax and lower neck anteriorly. He had suffered somewhat from dyspnea on exertion for about two months. Beginning in January, 1922, he had received x-ray treatment every two weeks for about one year, and then intermittently until March, 1924. He could not give any definite information about the details of the treatment.

Roentgenologic examination of the thorax disclosed "increased density over the left side to the level of the second rib, probably fluid." August 12 a gland was excised from the right supraclavicular space for microscopic examination, and this revealed Hodgkin's disease. A mass, approximately 6 cm in diameter, was found projecting from the left submaxillary triangle. Adjoining this mass below the angle of the jaw on the left side was a smaller nodule approximately 2.5 cm in diameter. In the subcutaneous tissues over the lower thorax posteriorly on the left side was another mass, 5 cm in diameter, but rather flattened, and fixed to the deep fascia. There was also adenopathy in the left supraclavicular, right anterior cervical, in both axillary, and both inguinal regions, and the veins of the abdomen were slightly distended.

A course of combined radium and x-ray treatment was planned, the radium to be directed to the large left submaxillary tumor in order to hasten its regression as much as possible, and the x-ray treatment to be directed to every other part of the neck, to both axillary and to both inguinal regions, as well as to the adenopathy in the mediastinum and in the lumbar region which was undoubtedly responsible for the gastric symptoms. Owing to the patient's general condition and dyspnea, the treatment could not be given at high voltage, but moderate voltage was used between August 14 and 19, the dosage being voltage 135 per K V the distance uniformly 16 inches. The cervical, axillary and inguinal regions were treated with 4 mm of aluminum filtration, 5 milliamperes for twenty-two minutes. The mediastinum was cross-fired from both front and back, and the presvertebral lymphatic

groups were attacked from behind only, with the same voltage and distance, but with filtration of 6 mm of aluminium, each field receiving 5 milliamperes for forty minutes. At the completion of the  $\alpha$ -ray treatment, the reaction was rather disagreeable, and the patient decided not to take the radium then but to go home. When he returned September 4, the fluid in the chest had diminished spontaneously, and the adenopathy present at the time of his first examination had largely subsided.

*Comment*—The interesting fact in this case is not so much the effect of  $\alpha$ -ray treatment on the adenopathy, because, as radiologists well know, such effect is uniformly to be expected and the reaction is usually quite rapid, but that the left submaxillary tumor, without any treatment, diminished in size from 50 to 60 per cent, in other words, the regression of this untreated lymphomatous tumor was nearly as pronounced as that seen in the other elements of the same process in other regions which had been subjected to  $\alpha$ -rays. Such a phenomenon has been reported, but I have seldom seen it manifested so strikingly. Of course, this patient is still under treatment and his condition is not completely under control.



## SEPTICEMIA DUE TO THE BACILLUS OF MORGAN NO. 1

THOMAS B. MAGATH AND EDNA JACKSON

The case reported here is of interest as, with one exception, it seems to be the first in which the bacillus of Morgan No 1 has been isolated from the blood stream. Kendall, Day and Bogg, in 1913, in their studies of summer diarrheas, described a fatal case from which *Bacillus dysenteriae* (Shigæ) was isolated from the stool, and a blood culture taken two days before death showed the presence of the *Bacillus dysenteriae* (Shigæ), *Bacillus paratyphosus B*, bacillus of Morgan No 1, *Bacillus alkaligenes*, and a streptococcus. The significance that could be attached to the finding of the bacillus of Morgan in the case of Kendall, Day and Bogg seems doubtful.

### REPORT OF CASE

A man, aged fifty-eight years, entered the Clinic February 19, 1924, complaining of hematuria. In 1920 he had had an operation for the removal of a tumor of the bladder, and for the repair of an inguinal hernia. In the meantime his general health had been good, and when he entered the Clinic he appeared to be well nourished.

The patient was thoroughly examined and taken to the hospital, February 26. On March 3 an operation was performed for recurring epithelioma of the bladder. The patient rallied fairly well after the operation, his temperature not rising above 99.5° until March 24. From that time on he suffered a high grade hyperpyrexia, with frequent chills (Figs. 226, 227). From April 1 the stools were loose, becoming extremely frequent, and containing a moderate amount of blood.

Blood cultures taken April 2 and April 8 disclosed the presence of a motile Gram-negative bacillus which produced acid and gas in dextrose, levulose, and galactose, not fermenting sucrose, lactose, mannite, dextrin, inosite, salicin, dulcite, tylose, raffinose, rhamnose, glycerin or inulin. Litmus milk was very slightly acid at the end of twenty-four hours, becoming alkaline in forty-eight hours or more. Gelatin was not liquefied and the tests for indol were strongly positive at the end of twenty-four hours. These cultural findings agree with those for the bacillus of Morgan No 1. A few days later, April 13, the same organism was isolated from the stool, and it

was the only organism found which could be considered pathogenic, all examinations for bacilli of typhoid, dysentery or paratyphoid were negative

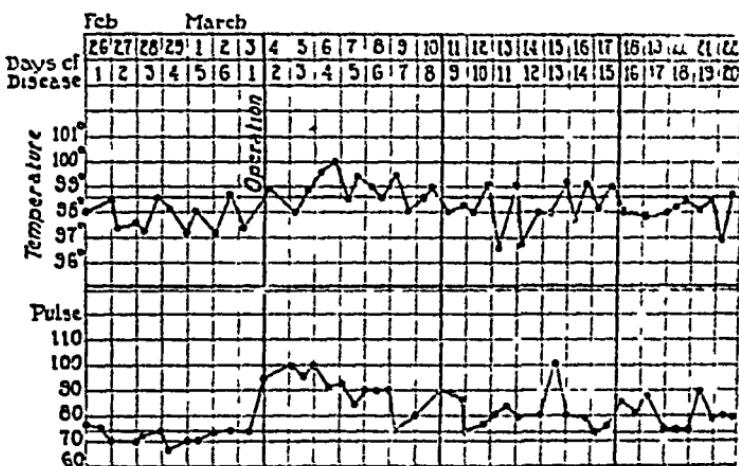


Fig 226—Record of temperature and pulse during hospitalization

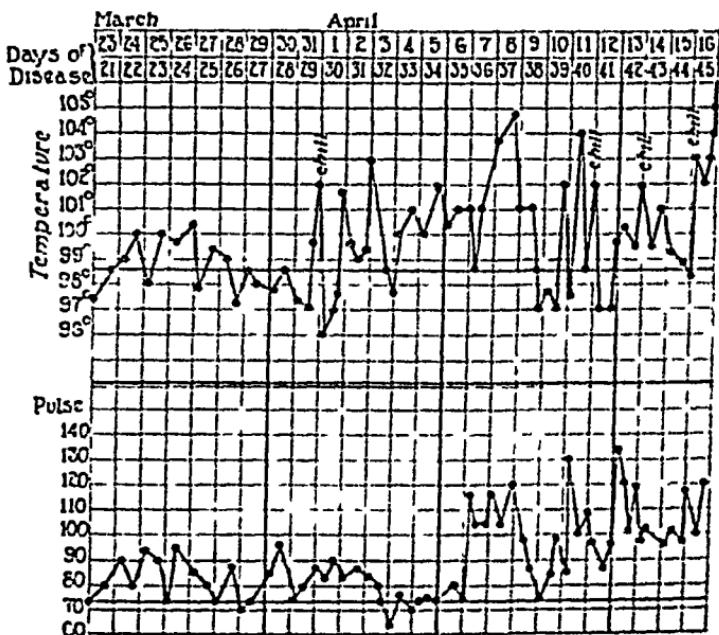


Fig 227—Record of temperature and pulse during hospitalization

After the organism was isolated from the first blood culture, agglutination tests with the patient's serum showed an agglutination in a dilution of 1

to 40 A rabbit immunized against this strain of Morgan's bacillus produced a serum showing agglutination of this bacillus in a dilution of 1 to 160

During the last two weeks of the patient's illness, he was extremely dull most of the time Only occasionally was it possible to rouse him to carry on an intelligent conversation He died April 16

At necropsy there was found a left recurring carcinoma of the bladder which had been operated on by cautery, and radium emanations employed There was a gangrenous cystitis and a right gangrenous uretero-pyelonephritis with pyonephrosis and atrophy, and metastasis to the inguinal and iliac lymph nodes Acute ulcerative colitis involved the colon (Fig 228) Following is the report of the pathologist on the findings in the colon



Fig 228—Photomicrograph of ulcers of the colon

"Throughout the colon, except in the right half of the transverse portion, are numerous irregular, rounded, oval and elongated elevations of the mucosa, from 5 mm to 1 mm in diameter, dark brown-red, mostly discrete, but occasionally confluent These areas have a granular surface, and are somewhat firm, with well defined edges where they join the normal mucosa. They are irregularly distributed with regard to the longitudinal bands, and are most numerous in the cecum, ascending colon and distal to the splenic flexure The mucosa in these elevated areas is markedly swollen, and thickly infiltrated, especially in the superficial layers, with red blood cells The epithelial cells, except in a few areas, have disappeared In the deeper

layers of the mucosa are numerous polymorphonuclear leukocytes, some lymphocytes, and necrosis. The submucosa is thickened and shows numerous ecchymoses, marked dilatation of the blood-vessels and infiltration with polymorphonuclears and some lymphocytes. Numerous slender bacilli are found in the superficial layers of the mucosa, in the submucosa and in the inner layers of the muscularis."

As a complicating factor in the diarrhea was the fact that mercurochrome 220 was administered intravenously April 6 and 13. This drug usually produces a diarrhea, which may even be bloody. However, since the patient had a bloody diarrhea five days before its administration, it must be concluded that some other factor was present to account for the diarrhea, and since the necropsy revealed definite ulcers in the colon, the diarrhea must have been of infectious origin.

The conclusion seems warranted, therefore, that the infection was due to the bacillus of Morgan No 1, that this produced a general septicemia and an ulceration of the colon, that it accounted for the patient's diarrhea, and is therefore a pathogenic organism for man, at least under certain conditions.

#### DISCUSSION OF LITERATURE

Morgan, in 1905, studied the intestinal bacteria in an epidemic of acute infantile diarrhea, in London, and isolated a bacillus which has since been known as the bacillus of Morgan No 1. Stools from fifty-eight cases were cultured and 304 cultures examined. Every organism which did not ferment lactose or liquefy gelatine was studied in detail. When the cultures had been run through various mediums, it was found that there were fourteen different strains that did not ferment lactose. Of these the so-called No 1 was by far the most numerous, being found in twenty-eight cases, No 2 was found in three cases, No 3 in five, and No 4 in two. The others were less common. None of these organisms corresponded with any known forms of pathogenic bacteria except No 6 and No 7, which culturally were like *Bacillus paratyphosus* or *Bacillus enteritidis*, but were not agglutinated with either of these serums. No 3 and No 4 were apparently closely related to members

of the typhoid-dysentery group Other bacteria were isolated frequently from drinking water, and no importance was attached to them

Of the fifty-eight cases studied, twenty-eight had been diagnosed clinically as acute infectious diarrhea, and thirty as catarrhal diarrhea From twenty-eight cases the bacillus No 1 was isolated from the stool and in seventeen of these it was the only organism present which did not ferment lactose In other cases it was accompanied by *Bacillus enteritidis* or *Bacillus paratyphosus* Later, stools of twenty normal children were examined; the bacillus of Morgan No 1 was isolated but once, and this strain did not wholly agree with the bacillus found in the other cases in that it produced less indol and made litmus milk less alkaline The following year Morgan continued his studies of infantile diarrhea, and isolated this organism from twelve of twenty-seven cases diagnosed as acute infectious diarrhea, and from three catarrhal cases

Morgan described this bacillus as being Gram-negative, motile, slightly smaller than the bacillus of typhoid, and producing acid and gas in dextrose, levulose, and galactose, but not fermenting mannite, dulcite, maltose, dextrin, lactose, sucrose, inulin, salicin, or arabinose It produces indol quickly, even in the presence of an excess of dextrose It does not liquefy gelatin, and in litmus milk it produces an alkaline reaction

When testing the pathogenicity of the organism obtained from his isolations, Morgan selected No 1, No 3, and No 4 When No 3 and No 4 were fed to rats, they died, although no diarrhea was produced With No 1 eighteen successful feeding experiments were conducted in which twelve young rabbits and six young rats were used Death took place after a severe diarrhea In each case the bacilli were recovered from the spleen, and in a few cases from the heart's blood Intravenous injections of No 1 gave negative results When the strain obtained from the stools of a normal child was used, no ill effects were noted, although a dose was given which was generally fatal if taken from cultures of diarrheal cases

Since this organism occurred so frequently in the cases

of diarrhea studied, and since it possessed a definite pathogenicity for rats and rabbits, Morgan was convinced that the organism was pathogenic for man, and that it was an etiologic factor in the type of infectious diarrhea encountered in England.

In testing the agglutinating reactions of the various strains isolated from his cases Morgan found that the organism was rarely agglutinated by the patient's serum, and that the different strains were not all agglutinated by any one immune serum, and usually only by an homologous serum.

Since Morgan's work (1905-1906) various investigators in Europe and in this country have isolated this organism. It has been found in the stools of patients with diarrhea, and has also been found by different investigators in cultures of stools from normal children and adults (Logan, Lewis). Frequently it has been associated with other bacilli of the typhoid dysentery group, such as *Bacillus dysenteriae*, *Bacillus enteritidis*, or *Bacillus paratyphosus*.

Thjøtta found that with his strains there was no agglutination with patients' serum and practically no cross agglutination with immune serums.

Kluger used seventeen strains which were culturally identical, and found that in antigenic properties they differed widely. Lewis, in 1912, tested 242 strains from 167 cases and found that as far as agglutination reactions were concerned, these fell into several groups, and that there was no constant relation between the source of the strain and its antigenic properties. Because of the facts that the organism has been isolated from stools of normal adults and children, that it is not agglutinated by the patient's serum, and that the various strains differ so widely antigenically, different investigators (Davison, Klugler) in this country question the etiologic relationship of the organism to infectious diarrhea. However, cases have been reported in which the organism has been isolated, and in which, in spite of great effort, no other etiologic factor has been found. Rey, in 1902, reported such a result in a case of fatal dysentery. The bacillus of Morgan No. 1 was isolated from the stool, the cultures being negative for bacilli of dysentery, typhoid or

paratyphoid. Examinations of the stool for amebæ and other parasites were negative. The patient died three weeks after admission to the hospital. The examination at necropsy disclosed involvement of the transverse colon, which contained a large amount of opalescent, fluid-like, dirty pus, the interior was disorganized and friable, with a multitude of large and small ulcers, none of which had perforated. No peritonitis was found except in this involved portion.

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# THE RÔLE OF FUNCTIONAL TESTS IN THE STUDY OF DISEASES OF THE LIVER

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An element of certainty characterizes opinions concerning disease of the kidney, which is lacking in those concerning disease of the liver. With regard to diseases of the kidney, certain routine helpful clinical and laboratory criteria have been established, but analogous criteria are not available in the realm of diseases of the liver. Great efforts are being made in various medical centers to improve the methods of investigating diseases of the liver, particularly with regard to the determination of its functional capacity. Data may be derived from a variety of sources, as follows:

## METHODS OF DETECTING HEPATIC DISEASE

**History and physical examination**—Local evidence, (1) pain and tenderness in the region of the liver, (2) increase in size, and (3) decrease in size. General evidence, (1) portal obstruction (hematemesis, ascites, collateral circulation, and enlargement of the spleen), (2) jaundice, (3) loss of weight, (4) loss of strength, (5) infection (chills, fever, sweats, and leukocytosis), (6) gastro-intestinal symptoms (indigestion, anorexia, nausea and vomiting), and (7) cerebral symptoms (depression, headache, delirium and coma).

**Routine laboratory studies**—Urinalysis for bile, urobilin, urobilinogen, and examination of stools for bile.

**Studies of duodenal contents**—Detection of bile pigments, bile salts, blood, and so forth.

**x-Ray examination of the gallbladder**.—With or without the use of dyes secreted in the bile.

**Studies of coagulability of the blood and fragility of the red cells.**

absence of diseases of the liver. However, the severity and nature of the disease are not so readily determined. In certain hepatic affections, syndromes either of an obstructive or toxic nature are ascribed to the liver. There is, however, no well-defined syndrome of insufficiency of the liver such as characterizes certain diseases of the kidney, heart, suprarenals and thyroid. In other words, the clinical picture and anatomic changes in the liver, even when definite, do not furnish an accurate conception of its functional changes, nor do they furnish reliable criteria concerning the outcome of such changes.

The unsatisfactory character of the information concerning the liver, obtained through ordinary routine clinical studies, is apparent to every thoughtful clinician. The desirability of extending our knowledge of the functional conditions in disease is indicated by the large number of tests devised and introduced for this purpose. I reviewed the earlier tests in an article in 1913, at which time the phenoltetrachlorphthalein test for hepatic function was introduced. A survey of all the more recent work has recently been made by Greene, Snell and Walters. From the large number of tests suggested, only those which are of special value will be discussed. These include our original phenoltetrachlorphthalein tests as modified by Rosenthal, the serum bilirubin determination by a modification of van den Bergh's method, the fructose tolerance test as utilized by McLean and his collaborators, and the hemokonia test of Brück. This discussion is based on experience in former years and especially on the work of the last year or so, carried on in the Mayo Clinic laboratories as group researches by Greene, Snell, Walters, McVicar, Eusterman, and others. The results of these studies will appear shortly in a series of articles on the subject.

Before presenting clinical cases, a discussion of the functional findings in experimental obstructive jaundice is desirable, in fact almost necessary, since jaundice, when it is present, usually dominates the clinical picture. Jaundice is also constantly associated with definite functional changes, as indicated by these functional tests. Indeed, jaundice itself constitutes a index of functional derangement of the liver or of the biliary passages.

## THE FUNCTION OF THE LIVER IN EXPERIMENTAL OBSTRUCTIVE JAUNDICE

Recent work by Bollman and Mann, and by Snell, Greene and Rountree has shown that ligation of the common bile duct after removal of the gall-bladder results in marked retention of serum bilirubin and phenoltetrachlorphthalein within twenty-four hours. The former rapidly approaches the level of 20 to 30 mg for each 100 c.c. of blood, and retention 4\* of the dye develops quickly. This retention is maintained more or less consistently until death unless the obstruction is relieved, when functional findings return to normal, except that of the phenoltetrachlorphthalein test. The latter continues to show slight retention, which probably indicates permanent hepatic injury. Positive values for sugar tolerance and hemokonia tests are practically constant throughout the period of obstruction.

Following ligation of the common duct with the gall-bladder intact, serum bilirubin 4 and dye retention 4 are reached about the third or fourth day. The indirect van den Bergh reaction appears first, followed later by the direct. Positive hemokonia and fructose tests are developed by the sixth day. The findings remain positive until death, unless the obstruction is relieved, in which case all the values tend to return to normal except that of the phenoltetrachlorphthalein test, which remains somewhat higher than normal, probably indicating permanent injury to the liver.

Van den Bergh, because of his recent studies on serum bilirubin, differentiates two forms of jaundice one exhibiting a direct and the other an indirect reaction for serum bilirubin, the former being designated as the mechanical type, and the latter the dynamic. McNee offers an ingenious hypothesis for the differences in the reactions of serum bilirubin, depending on whether or not the serum bilirubin has passed through the

\* A word of explanation is necessary in regard to our gradations of phenoltetrachlorphthalein. At the end of one hour, the amount normally present in the serum is from 0 to 3 per cent. Arbitrary findings of 3 to 10 per cent have been graded 1, 10 to 20 per cent, 2, 20 to 30 per cent, 3, and over 30 per cent, 4.

polygonal cells of the liver. He recognizes three types of jaundice: obstructive, toxic or infectious, and hemolytic.

The background, afforded by the experimental work referred to, is essential to the understanding of the functional findings in clinical conditions associated with jaundice. In all such cases it is important to know that the findings of these tests may be due to the mere retention of bile. In fact there is evidence accumulating to indicate that retained bile, *per se*, leads to marked alterations in function such as are indicated by these tests.

#### REPORT OF CASES OF DISEASES OF THE LIVER AND BILIARY PASSAGE

**Case 1** Gall-stones and cholecystitis — A man, aged seventy years, was admitted to the Clinic June 20, 1923, complaining of slight jaundice of ten days' duration. He had had six typical gall stone attacks since 1920, the last one three weeks before. Pain was referred to the back, was severe enough to require morphin, and in each instance the attacks were associated with jaundice.

Physical examination revealed slight jaundice, and tenderness and rigidity in the right upper quadrant. The urine contained bile. The blood was normal. The serum bilirubin was not studied, although a slight increase would be expected. The dye retention was slight, and the fructose tolerance test was positive. The clinical diagnosis was gall stones and cholecystitis.

Experience with these tests indicates that cholecystitis does not, as a rule, cause striking changes in the function of the liver. The degree of the functional injury in individual cases usually parallels the degree of the jaundice, provided hepatitis and cirrhosis of the liver can be excluded.

**Case 2** Infectious jaundice of the epidemic type — A man, aged twenty-nine years, came to the Clinic November 6, 1924, complaining of jaundice of one week's duration. He had had appendicitis in 1915 from which he had fully recovered, and had been well until two months before admission, when he began to have sore and bleeding gums, loss of weight, recurring anorexia, food distress, and nausea and vomiting for periods of two or three days. He did not have abdominal pain or tenderness. Two and one-half weeks before admission he again suffered with sore gums, sore throat, chills, malaise, fever, aching through the body, and anorexia. About ten days later he developed jaundice, tenderness over the renal area, distension of the abdomen and sclera, with dark urine clay-colored stools, and generalized pruritus.

At the same time, tenderness developed in the right upper quadrant and in the region of the kidneys posteriorly, but not actual pain.

Physical examination revealed icterus 3, and gingivitis 2. The liver was felt 2.5 cm below the left costal margin, and was slightly tender. The urine contained a trace of albumin, bile, urobilin and urobilinogen. The stools were light colored. The blood hemoglobin and counts were normal. The patient's physician had informed him that jaundice was prevalent in Buffalo, and that there was an epidemic there at that time. The functional tests revealed serum bilirubin 9.9 mg with a direct reaction, dye retention 4, and coagulation time nine minutes. Biliary drainage was instituted and used repeatedly. Bile was recovered in increasing quantities in successive drainages.

The clinical symptoms cleared up in the course of two weeks at which time the bilirubin had returned to 2.4 mg. The function returned to normal promptly with clearing up of the disease. This was a case of epidemic infectious jaundice with marked temporary derangement of the function of the liver, but the patient is now well.

**Case 3** Obstructive jaundice.—This man, aged thirty-four years, was admitted to the Clinic March 8, 1924, complaining of jaundice of mechanical origin from which he sought surgical relief. Tonsillectomy and appendectomy had been performed in 1912, and a gastro-enterostomy for duodenal ulcer in 1920. In 1923, because of cholecystitis, the gall-bladder was removed, but no stones were found. The patient said that pus drained from the biliary fistula for six weeks after the operation, then healing occurred and he was well until September 14, 1923. On this day he had thirteen stools, the last one clay-colored. Jaundice was then noted for the first time, it persisted, and became more marked, but varied somewhat in intensity as did the color of the stools. The patient had had a splendid appetite and had gained in weight, shortly before examination, although bloating and nausea had occurred at times lately, and weakness had developed.

Physical examination revealed icterus 4, tenderness throughout the epigastrium, the liver edge palpable and tender. The urine contained bile 4. The blood hemoglobin was 64 per cent, the erythrocytes numbered 3,890,000, and the leukocytes 10,900. The coagulation time was nineteen minutes.

The patient was treated preoperatively (according to Walters' method), and March 26, 1924, an exploratory operation was performed. Obstruction of the common bile duct was found and a reconstruction of the duct was made over a T tube. Studies of the function, made prior to operation, revealed serum bilirubin 24.8 mg, dye retention 4, and normal sugar tolerance, twelve days subsequent to operation, the serum bilirubin was 5.3 mg, and the dye retention 1. At the end of sixty-five days there was a decrease of the serum bilirubin to 2.5 mg and of the dye retention to 1. The patient returned October 25 with jaundice and evidence of biliary obstruction. The serum bilirubin was 5.2 mg and the dye retention 2. A choledochoduodenostomy was performed with excellent recovery. Prior to the patient's dismissal the serum bilirubin was 3.4 mg and dye retention 1. Sugar tolerance tests were normal on three occasions.

This represents a typical case of mechanical obstruction, and reveals the functional changes incident to obstruction and the effect of relief from it on the findings of the functional tests

#### TWO CASES OF CIRRHOSIS OF THE LIVER. ONE PORTAL AND ONE BILIARY

**Case 4** Early biliary cirrhosis with jaundice — A man, aged eighteen years, was admitted to the Clinic November 3, 1924, complaining of painless jaundice, which had begun two years before, with the appearance of icterus, dark urine, and clay-colored stools. He was attended by a local physician who made a diagnosis of catarrhal jaundice. In two months the jaundice began to clear up somewhat, but never entirely disappeared. It had been associated with slight itching, but otherwise the patient had felt well throughout his illness. A week or so before coming to the Clinic he underwent medical examination as a result of an application for a new position. The jaundice was recognized, and he was advised to come to Rochester. On clinical examination, jaundice was revealed, the liver margin was palpable 3 cm below the costal margin, but not tender, the spleen was easily palpable, there had been no loss in weight. The urine and stools contained bile. The blood counts were normal, the resistance of the red cells was normal or somewhat increased, and the coagulation time was slightly increased. Studies of the function of the liver revealed serum bilirubin 9.5 mg, but the reaction was indirect. The dye retention was 2, and the fructose tolerance test was positive. Biliary drainage was instituted and bile obtained. In tests made three or four days later, the serum bilirubin was 6.5 mg, the reaction being again indirect. The patient expected to continue treatment at home.

This case is an instance of jaundice in which obstruction is probably partial and intermittent. Hemolytic jaundice was considered, but excluded because of decreased fragility of the erythrocytes and also because of the existence of pruritis. This probably is a case of early biliary cirrhosis. Hanot's type is suggested by the age and clinical manifestations, but Hanot's cirrhosis is so poorly defined that in the Clinic its existence as a disease entity is questioned.

**Case 5** Portal cirrhosis with marked ascites — A man, aged sixty-three years, was admitted to the Clinic November 20, 1924, complaining of enlargement of the abdomen of two months' duration. About six months before, he had suffered somewhat from abdominal distress, bloating and diarrhea. Three months before, a hernia had been repaired. At operation the surgeon noted free fluid in the abdomen, examined the liver, and made a diagnosis of atrophic cirrhosis of the liver. A month later swelling of the

abdomen became noticeable, and two weeks later edema of the ankles. The patient had noticed a decrease in the urine since September 1.

Physical examination revealed ascites 4, with well established abdominal collateral circulation, pallor, emaciation and red, dry, parched tongue. The heart was pushed up, cardiac dulness measuring 11 cm in the second, and 13 cm in the third interspace. The lungs were clear, although the diaphragm was markedly elevated. Edema 1 and 2 was found over the ankles and sacrum. The urine was normal except for occasional traces of albumin, the blood hemoglobin was 55 per cent, the erythrocytes numbered 3,500,000, and the leukocytes 3,000. Studies of the function of the liver disclosed dye retention 3, and normal values for serum bilirubin.

Fluid and salt intake were restricted and the patient was given novasurol from 1 to 2 c.c. hypodermically, 1 c.c. intra-abdominally and 2 c.c. intravenously. These were administered at about four-day intervals, the total amounting to 82 c.c. in seventeen days. A marked diuresis followed these injections with the exception of that given intra-abdominally. The patient promptly lost more than 20 pounds. The ascites cleared up, as it had in two other cases of portal cirrhosis associated with Banti's disease, under this treatment. Whether or not the patient will get entirely well remains to be seen. However, the ascites entirely disappeared in the two other cases. In one it has not reappeared after six months, while in the other, sufficient time has not yet elapsed to permit an opinion. The spleen is definitely large in this patient also, and it is questionable whether Banti's disease can be positively excluded.

It is often impossible to diagnose cancer of the liver in its early stages. Marked and rapid enlargement of the liver, a nodular surface, glandular metastasis and rapidly progressing anemia with loss of weight and strength, all suggest malignancy, but these features usually appear later in the course of the disease. In their absence diagnosis may be impossible except by exploration. Functional changes, however, appear early in some instances and may actually prove of diagnostic value. The following two cases emphasize the difficulties of diagnosis in cancer of the liver and bile passages, and also the value of functional studies.

**Case 6** Obstructive jaundice, cancer of head of pancreas, metastasis to the liver, and cirrhosis of the liver.—A man, aged thirty-four years, was admitted to the Clinic August 26, 1924, complaining of painless jaundice of ten weeks' duration. He had had a chancre fifteen years before, and marked alcoholism, particularly excessive for three months prior to the present illness. Ten weeks before admission, he suffered from heart-burn, the urine became dark, and the stools light, two days later jaundice appeared. Diarrhea, and a foul taste in the mouth followed. The local physician ad-

ministered neo-arsphenamine and instituted duodenal drainage, obtaining fluid containing bile

Physical examination revealed that the patient was critically ill and markedly emaciated, having lost 30 pounds within three months. The pulse was 4. The liver was palpable to the umbilicus, but the gallbladder and the spleen were not felt. Urinalysis revealed bile 3; the stools were clay colored and gave a positive guaiac test. The gastric contents contained normal free hydrochloric acid. The hemoglobin was 60 per cent, the erythrocytes numbered 3,700,000, and the leukocytes 8,250. The renal function was normal as determined by blood chemistry. The serum bilirubin was 36 mg, and dye retention 4, while the fructose tolerance test was positive. Duodenal drainage failed to reveal bile, but blood was present in the intestinal secretions. The course of the disease was afebrile at first, but a few days after admission, chills and fever developed, the fever ranging from 102° to 104° until death occurred. As anemia progressed rapidly the patient was given a transfusion. Ten days after admission the serum bilirubin was 16 mg. Renal insufficiency developed, the blood urea amounting to 200 mg for each 100 c.c. of blood. Two days before death, the liver reached the umbilicus, and a mass, which was believed to be the gall bladder, could be felt and seen. A moderate grade of ascites developed.

The clinical diagnosis was obstructive jaundice, cholangitis, hepatitis and cirrhosis. Necropsy was refused, but partial examination revealed carcinoma at the head of the pancreas with metastasis to the liver, and cirrhosis.

Because of the history of chancre, syphilis was suspected, but was excluded on account of the negative serology. The striking history of alcoholism suggested the possibility of cirrhosis in the hypertrophic stage. The profound toxemia and general infection, with the biliary obstruction, suggested cholangitis and hepatitis. Cancer was suspected, but thought to be unlikely by most of the consultants, including myself, who studied the patient. Unfortunately this experience is far from being unique in cancer of the liver and bile passages.

**Case 7** Carcinoma of the gall-bladder with metastasis to the liver—A woman, aged forty-six years, was admitted to the Clinic June 4, 1924, complaining of attacks of pain in the right upper quadrant, and fever, lasting eight months. She had had typhoid fever in 1915. The present illness began in November, 1923, with an attack of severe pain in the right upper quadrant, radiating to the lower abdomen. At this time the patient was in bed for two or three days, she obtained relief by the administration of castor oil.

Physical examination revealed an egg-shaped mass below the right costal margin, which later disappeared. The attacks had recurred at intervals of two or three weeks, the mass persisting after January, 1924. The liver edge became palpable, the course of the disease became febrile, the temperature

reaching 102°, and weakness and loss of weight ensued. There was no jaundice. The liver was enlarged, being palpable 8 cm below the right costal margin, a rounded mass, supposedly the gall-bladder, was also palpable. There was no glandular enlargement. The urine contained a trace of bile. The hemoglobin was 65 per cent, the erythrocytes numbered 3,800,000, and the leukocytes 19,200. The coagulation time was fifteen minutes. The stools were negative for bile. The renal function was normal, as indicated by blood chemistry. The serum bilirubin was 1.6 mg, the dye retention 3, and the fructose tolerance test negative. A diagnosis was made of cholecystitis with stones and empyema of the gall-bladder.

Operation revealed gallstones and cancer of the gall-bladder with extensive metastasis to the liver. In all probability infection was responsible for the febrile course of the disease. The pathologists reported squamous-cell epithelioma of the liver, and adenocarcinoma of the gall-bladder.

The history in this case is very suggestive of gall stones. Gall-stones, *per se*, do not cause marked functional changes unless they cause jaundice. In both cases the phenoltetrachlorphthalein test indicated marked changes in hepatic function, while the serum bilirubin findings were in keeping with either the presence or absence of jaundice.

#### DISCUSSION

In 1914, as the result of studies on the function of the liver, the conclusion was reached that the information derived from these studies does not compare in diagnostic and prognostic importance with that from corresponding studies of renal function. This was thought to be dependent on several factors (1) the limited number of cases of severe hepatic involvement studied, (2) the fact that hepatic function may be carried on efficiently with but a small portion of hepatic substance, the factor of safety being unusually great, and (3) the fact that the prognosis in many cases is controlled by factors other than decreased hepatic function, *per se*, that is, myocardial insufficiency, carcinoma, and syphilis. The uncertainty in the prognosis was thought to be due to lack of correlation of anatomic, clinical and functional findings occasioned by the newness of the subject investigated. However, it was firmly believed that, scientifically and clinically, this subject was worthy of much more extensive investigation. Today, after ten years, these conclusions still

stand. In the interim, however, notable progress has been made. The findings of the tests in hepatic disease now have more than mere academic value. The introduction of quantitative methods for the determination of serum bilirubin and improved methods of utilizing phenoltetrachlorphthalein have made available two practical procedures which yield information of considerable clinical significance. Furthermore, jaundice itself has been rendered available for study so that the scope of application of these tests has been broadened considerably. There is at present a great need, however, for an adequate method for determining the bile salts in the blood. This in turn will permit of a direct approach to the problems of dissociated jaundice.

Studies of the function of the liver yield information of a quantitative nature, and though at present they do not yield information which measures up in diagnostic and prognostic importance with that in corresponding studies of renal function, yet when considered in conjunction with the clinical history, physical examination, and other laboratory findings, this information is frequently of great significance and permits of conclusions with regard to the extent of functional injury. By repetition of the test, the degree of injury in hepatic disease may also be followed more or less quantitatively. The various tests, in all probability, pertain to different functions of the liver and consequently yield broader information than can be obtained from a single test of one function. While in obstructive jaundice, the serum bilirubin and dye retention tend to parallel each other during any great fluctuations in the degree of jaundice, in certain other forms of hepatic disease the dye retention may be maximal, while the serum bilirubin is excreted normally and fails to accumulate in the blood.

Latent injury to the liver often is revealed, especially in certain diseases associated with a subicteric tint of the skin such as pernicious anemia. The van den Bergh test is capable of revealing the existence of latent icterus. More important, however, from the practical point of view, is the detection of metastasis to the liver through the discovery in certain instances of decreased hepatic function in which detection would be other-

wise impossible. Although functional tests will probably fail to reveal the very earliest hepatic involvement, yet experience suggests that they often indicate involvement of the hepatic function when other clinical studies are inconclusive. In this connection valuable information has been elicited with regard to metastasis to the liver in many of our cases of carcinoma of the stomach, of the sigmoid, and so forth.

Finally, functional studies disclose changes in function in relation to therapeutic procedures. In the treatment of syphilis, for instance, injury to the liver can often be determined prior to the actual onset of jaundice. The effect of treatment on hepatic function as determined by the tests, affords an index to the most desirable type of treatment, and the extent to which it may be forced with safety. Functional and clinical improvement occur after administering glucose or sodium chlorid in cases of hepatic insufficiency. Unquestionably the tests will play a similar part in the treatment of other diseases of the liver. For example, a serious effect on hepatic function has been demonstrated by one of the laboratory staff following the administration of chaulmoogra oil to dogs, while in many instances prompt improvement in the findings of the test has followed surgical or medical procedures.

From the foregoing, it appears that although studies of the function of the liver so far have failed to equal in value similar studies of the function of the kidney, yet they are already of definite and considerable practical importance. The progress in the last fifteen years has been notable. With the development of better methods functional studies of the liver will unquestionably occupy an important place in clinical medicine.



